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Several research goals were accomplished during the four years of this grant. We found that the responsiveness of primary somatosensory (SI) cortical neurons is "unattenuated" if when behavioral conditions become unpredictable and that SI neurons responding to sensory cues for wrist movement with the greatest fidelity have their activity modulated just prior to movement onset. These observations fits with the hypotheses that during predictable and stereotyped behaviors, neuronal responsiveness is gated so that the CNS may partially engage in other activities and that sensory inputs that are no longer behaviorally relevant are gated so as not to interfere with monitoring movement parameters by the primate CNS. We also found that human subjects can improve in their ability to perform simple motor tasks and that the improvement can be modeled to predict which subject will eventually be good performers after only a few days of training. Moreover, the initiation of intended movements can be interrupted by tactile abort signals given prior to movement execution if these signals are given in the proper manner.

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RESEARCH OBJECTIVES

General goals of these studies were a) to understand the influence of behavioral unpredictability and knowledge of results upon sensorimotor cortical activity, b) to understand the special role that these neurons play in sensorimotor integration during the initiation and execution of movements and c) to determine, eventually, if human subjects perform the behavioral tasks in a way that strengthens the contention that neurophysiological events in the primate brain reflect what occurs in homologous regions of the human CNS while performing under the same behavioral conditions.

Several research goals were accomplished during the three years and one year of no-cost extension of this grant. 1) Analysis of data indicated that the responsiveness of primary somatosensory (SI) cortical neurons becomes "unattenuated" if when behavioral conditions become unpredictable. This observation fits with the hypothesis that during stereotyped behavior, neuronal responsiveness is gated so that the CNS may partially engage in other activities. 2) SI cortical neurons that respond to vibratory go-cues for wrist movement with the greatest fidelity have their activity modulated just prior to movement onset. This observation fits with the hypothesis that prior to active movement, sensory inputs that are no longer behaviorally relevant are gated so as not to interfere with monitoring movement parameters by the primate CNS. 3) SI cortical neurons that may bind together other SI neurons with their rhythmic activity have this activity disrupted at go-cue onset and just prior to movement onset. This observation fits with the hypothesis that prior to behaviorally significant events, the activity of these neurons that may tonically gate other SI neurons is suppressed to allow the monitoring sensory event and the initiation of movements. 4) Recent observation suggest that entrained and non-entrained high frequency vibratory sensitive (HFVS) neurons, which constitute ~4% of task related neurons, belong to different hierarchical stages of information processing. For these neurons, movement-associated changes in activity occurred earlier than movement onset, but, in most instances (~80%), occurred later than the onset of electromyographic activity of forearm muscles. Therefore, these activity changes could result from peripheral inputs. 5) Results of human psychophysical experiments indicate that visually guided movements are performed more quickly when a vibratory signal to the hand that is to be moved is presented in conjunction with the visual target. They also indicate that movement times, though somewhat faster without the presence of vibratory stimuli that lasts until the target has been reached, are not significantly different as a function of the type of go-cue that a subject receives. These studies suggest that a paradigm of the sort described below could be used to assess the potential performance of individuals on precision wrist movement tasks. 6) Recent findings suggest that human subjects can alter wrist movements toward a positional target if vibratory abort-cues are presented early enough. Correct alterations in movement become more likely with increased practice. Final performance and the time necessary to achieve it range on the order of 4-6 days.

Each study will be described following a general outline of the background that lead to the design of the studies to be described below. Some of the work has either been published or has been submitted for publication and is undergoing review.

Background

Active movement involves stimulus detection and classification, as well as response programming, selection and production. Moreover, proper motor control also involves the use of information about external environmental conditions and the current "internal state" of the parts of the body that will be moved. The availability and utilization of sensory information about both the internal and external behavioral and environmental states are subject to alteration by the attentional system, which, by Posner and Petersens's definition, is responsible for "...a) orienting to sensory events; b) detecting signals for

focal (conscious) processing, and c) maintaining a vigilant or alert state". In addition to attentional factors, it seems important to add intention to move and emotional constituents (e.g., expectation of successful behavioral outcome) to the list of factors influencing motor performance. Finally, the internal representations of current behavioral circumstances, as they relate to impending actions, must be updated efficiently to account for any changes in conditions that could affect movements waiting to be planned or executed if previously programmed. Each concept is based upon the knowledge, available through introspection, but difficult to prove scientifically, that "much information is continuously transmitted by sensory receptors from the environment to the brain, but only a fraction of this information is consciously perceived at any one time".

Previous studies have demonstrated several basic principles regarding the influences of behavioral context upon sensory responsiveness and ultimately upon sensorimotor integration. We based our studies on these principles. First, it is usually presumed that there is a behavioral "steady state" achieved during performance of necessarily over-trained and stereotypic behaviors. Changes in sensory responsiveness and motor performance are referenced to this baseline. Second, regions of the CNS involved in sensorimotor integration are more responsive to inputs when animals or subjects are actively engaged in the task. Responses to inputs presented passively are diminished in comparison. Third, more complex behavioral requirements, such as discrimination rather than mere detection of inputs, engage the sensorimotor integration system even more. This results not only in changes in signal-to-noise ratio during the initial phases of a behavioral trial, but may also result in responsiveness modulation prior to response onset to "readjust" certain parts of the system for their participation in response programming, selection and production. Fourth, nearly identical behavioral responses can be made over a number of behavioral trials and these responses can be elicited by several types of go-cues provided that these cues are selected carefully and the animals or subjects adequately taught to make proper responses. Thus, subtle effects of continuous stimulus presentation and possible effects of stimulus interference with response programming, selection and production can be determined. Finally, while the source of the central influences which maintain response integrity and regulate sensory inputs is not known, these influences are probably mediated through the motor cortices.

As our working hypothesis, we suggested that corollary discharge from motor cortical areas is the intermediate source of the inputs that result in sensory responsiveness modulation in SI. Recent studies have shown that motor intracortical microstimulation can alter SI evoked responses and suggest that neuronal sensory responsiveness is altered by the same mechanism. In addition, neurons in motor, premotor and parietal cortices, recorded during behavioral tasks similar to ours, are activated at times (>100ms before movement) that could account for our observations regarding premovement activity (PMA) onset. These cortical regions have preparatory neurons that encode the goal or target and the intended direction of movement independent of their movement-related discharge. Changes in somatosensory inputs to MI are said to be sufficient to reorganize MI outputs thus emphasizing the importance of sensory inputs for maintaining the organization of the motor system, which, in turn, may regulate sensory responsiveness. However, premotor and MI cortices may have different capacities for response plasticity since the proportion of cue-related responses in premotor cortex increases with extended learning while it does not in MI. It is not known if these effects form the substrate for SI modulation or may result from changes in SI responsiveness. It is certainly not known if these same neurons show trial-by trial modulation when a learned task becomes suddenly unpredictable. Since it is difficult to follow sensorimotor cortical neurons during learning, we propose instead to examine these neurons in the same animals when the security of the associations between cues and movements are unpredictably altered. Finally, many neurons in motor and premotor cortices have characteristics that fit suggested components of a model we developed to account for PMA and sensory responsiveness modulation in SI. We wish to gain data from motor and premotor cortical neurons to determine if the timing of their influences adds to the validity of the model or suggest changes in it.

STATUS OF CURRENT RESEARCH

Statement of Work

We derived experiments to test the hypothesis that SI neuronal activity, related to stimulus detection, and movement initiation and execution, changes markedly when animals must use vibrotactile signals to guide their behavior. This hypothesis is based upon the observations that motor dysfunction, such as in basal ganglia disease, is often accompanied by impairment in proprioceptive regulation, that visual cues can ameliorate some performance deficits and that many of the cortical neurons that have the most profound changes in sensory responsiveness have deep receptive fields. It is based upon a slight modification of the second and third of Matthews' tenets regarding corollary discharge, that is, the assumption that this discharge is generated only if necessary and then at a time, of a polarity and of a magnitude to gate potentially interfering peripheral inputs resulting from ongoing palmar vibration. Finally, it is based upon the assumption that requiring the use of peripheral information in sensory guidance will increase the selective attention directed toward inputs carrying that information. It assumes comparable behavioral responses will be made under different sensory cueing conditions. Thus, motor-set was not altered significantly in the experiments that will be described. Our goal was to record from area 3a, 3b and 1 neurons initially and to then record from neurons in areas 2,4,5 and/or 6 as time permitted. The rationale for recording in anterior and central SI is that these cortical areas are known to respond well to the stimuli that will be used for the guidance cue. The rationale for recording from the latter cortical areas is essentially the same as listed above.

Research Design and Methods.

Preliminary results indicate that a significant percentage of SI neurons show markedly different response profiles associated with the behavioral context in which peripheral stimuli are delivered and wrist movement made. Alterations in activity are related to whether monkeys make movements in response to sensory inputs that are delivered to the same body part that is subsequently moved and whether a reward for these movements is predictable. Many sensorimotor cortical neurons are characterized by decreases or increases in firing rates that occur before movement onset and before changes in EMG activity, suggesting that they receive central as well as peripherally generated modulatory inputs. Centrally generated influences may be different depending upon RF type, handle loading conditions and movement direction of with respect to the stimulated hand surface.

Two types of experiments were used to gain additional information about changes in sensorimotor cortical neuronal activity in monkeys and the relationship of these changes to those that probably occur in humans. First, the general features of the monkey behavioral tasks will be described, followed by a description of the surgical, recording procedures, data collection, histological and penetration reconstruction procedures. Next, the specific tasks used with monkeys will be described followed by the specializations in data analysis to be used in these experiments. The human psychophysical experiments used similar behavioral paradigms. The human experiments assessed behavioral capacities by measuring RTs and MTs. RTs and MTs from each of the monkey experiments were measured daily.

This approach provided a unique opportunity for human and subhuman primate behavior to be compared. Comparison of human and subhuman primate behavioral performance on similar tasks strengthened the contention that neurophysiological events in the primate brain reflect what occurs in homologous regions of the human CNS while performing under the same behavioral conditions.

Experimental Methods - Monkeys: Training and Surgery

Adult male rhesus monkeys *(Macaca mulatta)* were trained to perform a stereotyped sequence of behaviors while seated in a monkey chair. Each will be cared for in accordance with the *NIH Guide for Care and Use of Laboratory Animals, revised 1985*. Each monkey's forearm was restrained just above the wrist and at the elbow with velcro straps. Each animal's right hand manipulated a smooth aluminum plate attached at one end to the axle of a brushless DC torque motor. The manipulandum was placed directly beneath the wrist joint thus allowing flexion and extension of the pronated hand about the wrist. A constant torque of 0.07 Newton-meters (Nm) was applied in the upward direction requiring the animals to exert a flexion force to maintain the plate in a centered position corresponding to neither flexion nor extension of the wrist. A constant force of 0.07 Newton-meters was generated by the motor (Vernitron model VBTMH38-B1) which was under feedback control by circuitry that controls the motor's power supply (Kepco BOP 36-5M). The position of the handle attached to the axle of the torque motor was sensed by a rotary variable differential transformer (RVDT - Pickering model 23380) in series with the motor's axle (23). Visual feedback of the handle position normally was displayed to the monkey by an LED panel with the central LED, corresponding to the centered handle position, different in color and size from the remaining LEDs. The feedback system was calibrated so that each successive LED above or below the center lamp is illuminated for a 1° change in handle position in that direction from the center zone.

Behavioral tasks will be described below. Upon successful completion of a reward trial, a fruit juice reward was given to the previously fluid deprived animals. The body weight of each animal was monitored daily. Care was taken to supplement the experimental fluid intake to maintain the animal at 90% of the normal body weight. When the animals did not perform, water was available in their cages.

After animals reached reliable task performance, surgery was performed at the University's Department of Comparative Medicine under the direction of the University's veterinary staff. Monkeys were maintained at a surgical level of anesthesia with a nitrous oxide/oxygen mixture along with Isofluorane®. Proper facilities for artificially respirating the animals and monitoring expired carbon dioxide were used as needed. Each animal's electrocardiogram was monitored. A scalp incision was made and the temporalis muscle reflected over the region of the left parieto-frontal cortices. A craniotomy was performed so that a passivated stainless steel recording chamber could be implanted over the craniotomy. These oval chambers are made of 316-L stainless steel and have internal dimensions of 18mm by 36mm. The chamber was stereotaxically placed on the skull at an angle of 45° from true horizontal, with its anterior margin located at AP +16, centered at LM +14, by the coordinates of Olszewski with appropriate correction factors for the actual size of each experimental animal. This placement allowed access to the vast majority of the sensorimotor cortex. Stainless steel skull bolts were implanted at four sites and used for head restraint during recording sessions. The chamber and bolts were secured to the skull with surgical acrylic cement (Howmedica; Surgical Simplex P®).

The wounds were closed in layers after incisions were made to allow the chamber and the bolts to pass through the scalp. Topical antibiotics were applied to the wound margin. Systemic antibiotics were given following surgery and a small amount of intrathecal strength antibiotic was placed in the sealed chamber to guard against infection. Complete blood counts were done initially and periodically to monitor the animal's progress. Care was taken to eliminate any pain experienced by the monkeys.

Electrophysiological recording sessions.

Recording electrodes were fabricated in the laboratory by placing platinum-iridium wire (Engelhard

Industries Div.) in 28-gauge hypodermic tubing and then placing that inside another, larger piece of tubing. The first prevented the fine wire from deviating extensively during the course of the penetrations; the second secured the electrode to the chronic microdrive. The platinum-iridium wire was etched to a fine tip of approximately 2-5 μm by passing alternating current through it while it was immersed in a bath of Clorox®. A relatively coarsely tapered electrode profile was necessary for the transdural penetrations. Electrodes were coated with molten glass distally and Epoxylite (Epoxylite International) proximally. Electrode tips were exposed electrically by pulsing a DC voltage across the tip. Electrodes with impedances at 1KHz of 0.9-2.5 MΩ were routinely made and used for neurophysiological recording.

During each recording session, a glass-coated platinum-iridium microelectrode was positioned over the pre- or postcentral cortex by means of microdrive with a x-y stage (Narishige MO-95B) attached to the saline-filled sealed chamber. The electrode was manually advanced through the dural surface. The initial depth of the cortical surface was used later in the reconstruction of penetration sites. The electrode was then be advanced in small increments into the ipsilateral sensorimotor cortex.

Extracellular recordings of the activity of single cortical neurons were made while the monkeys perform behavioral tasks by conventional means. Recording sessions normally last between 2-6 hours and were immediately terminated if the animal showed any signs of discomfort or did not perform the task. Experience over the last nine years indicated that monkeys routinely perform for this duration and were highly motivated. As warranted, the recording sites were micro-stimulated (train of 11 cathodal pulses; 200 μsec pulse duration at 330Hz, intensity <=60 μA, one train per sec for at least 1 minute) to determine if there were noticeable microstimulation effects. Before and after each session, the recording chamber was flushed with sterile saline. After recording, the chamber was filled with saline, antibiotics added, and the chamber sealed with a TEFLON® cap. The monkeys were then be returned to their home cages.

Data collection.

The activity of single cortical neurons was recorded during behavioral task performance. Potentials recorded by microelectrodes were routinely amplified and filtered and displayed on an oscilloscope. The oscilloscope is triggered by the initially negative unitary potentials associated with neural spikes recorded at a safe distance from the soma. Spikes of individual neurons were discriminated using atime-amplitude window discriminator.

Data were collected by an on-line data collection routine for real-time events, run by a PDP11/23+ microcomputer. Digitized pulses of single neuronal spikes were entered into the data stream via parallel input lines, interrupting the computer and causing the real-time clock to be read so that the time of occurrence was recorded with resolution of 100 microseconds. Analog signals corresponding to the handle position and hence the location of the animal's hand were sampled at 100-400Hz by an A/D converter. The computer, which controled the behavioral paradigm, also entered information about real-time task execution, coding each unique event and branch point decision and enters these into the data stream.

At regular intervals, EMG recordings of the forearm muscles acting across the wrist were made, sometimes simultaneously with sensorimotor cortical recordings. Intramuscular EMG wires (stranded stainless steel, TEFLON® insulated; Bergen Wire Rope Co.) were temporarily implanted in muscles using sterile 25 gauge needles as guides. The EMG activity were rectified, integrated and then digitized by the on-line data collection routine. The goal was to correlate neural activity with specific movement- and stimulus-related events.

Once the activity of each neuron was recorded during performance of the behavioral task, the peripheral RF of each neuron was examined by probing the skin with a Rowan anesthesiometer, palpating bellies and manipulating joints. Off-line data analysis and display routines were run for the recordings of each neuron. These laboratory generated 486 PC-based programs allowed the simultaneous graphic display of digitized neural events and the hand position and produce hardcopies. Thus, changes in neuronal firing rate could be correlated with changes in hand position. Examples of the output of this program are seen in Figures 2-4 and 6.

Histology and penetration reconstruction.

After the final recording session, each animal was anesthetized with ketamine hydrochloride (33mg/kg) and a microelectrode placed in the cortex, in turn, at each of several points of interest. Small electrolytic lesions were made at each point of interest by passing anodal current (10μA, 20 sec) through the recording electrode. After the animal recovered from the anesthesia, it was allowed to survive for 2 days. Then the animal was given a lethal dose of Pentobarbital and perfused intracardially with saline followed by 10% buffered formol-saline. Prior to removing the brain from the skull, it was blocked stereotaxically. The brain was removed from the skull, and cut on a freezing microtome in 50 μm sections in a parasagittal plane orthogonal to the plane of the electrode penetrations.

Locations of penetrations and recording sites within each tract were determined by considering a number of factors. Surface photographs of the experimental hemisphere were taken and the location of each penetration determined by reference to the stereotaxic blocking marks made at known chamber positions. Enlarged scale drawings of each brain section containing penetration tracts were made using a microprojector or were made by digitizing sagittal sections. The location of each tract was usually evident in histological material. Each recording site was located by computing the recording site depth from surface along the penetration tract as reconstructed on scaled drawings, corrected for any shrinkage by adjusting the scale by the difference in the distance between the marking lesion tracks before and after sectioning the material. The cytoarchitectonic location each recording was determined by comparing each site with the morphological characteristics of the sensorimotor cortices by criteria established previously. Only data from reconstructed recording locations was used in the analyses. In this way, the functions of each of the subregions that comprise the primate sensorimotor cortices could be evaluated by the response of their neurons recorded during the performance of the behavior tasks.

Behavioral Paradigms.

Reward Predictability and Cortical Neuronal Activity - "The Unpredictable Task"

This task consisted of three basic parts: maintenance of an initial wrist position, detection of a vibratory cue delivered to the palm of the hand or a visual cue and ballistic wrist flexion or extension movements. Each trial began when the monkey positions the handle in the centered zone, thus actively holding the handle in that position against a small upward force generated by a DC torque motor (see above). The monkey held this centered position for a period equal to 0.5, 1.0, 1.5 or 2.0 sec (pseudo-randomly varied, based on a computer random number generator). If the animal moved prior to the completion of the hold period, the trial was cancelled. The monkey could initiate a new trial by returning the handle to the central zone.

If the monkey did not move during the hold period, in some trials the plate, at times, was vibrated, signaling the monkey that the movement could begin. The vibratory cue was delivered by adding a sine

wave signal generated by a signal generator to the summing junction of the operational amplifier in the torque motor controller which was also involved in steady state torque production. The amplitude of vibratory signals was <0.057° or less than 100 μm peak-to-peak measured 10cm distal to the coupling of the handle to the motor. This amplitude was sufficient to excite cutaneous receptors in the palm and fingers. Three stimulus frequencies were tested; 27, 57 and 127Hz which excite cutaneous rapid adaptors, both rapid adaptors and Pacinian afferents, and probably only Pacinian afferents, respectively. Higher frequencies are also known to excite muscle spindles. Visual go-cues were the illumination of one of several LEDs away from the center LED and indicated the direction of the wrist movement that must be made. Rewards of fruit juice were given by a solenoid-based system ("juicer"), controlled by the computer

Unless sttated specifically in the description of the results, all correctly performaed trials were rewarded. In the single study in which reward was varied, correct performance was rewarded only 75% of the time (partial reward). In the other 25% of the correctly performed trials (pseudo-randomized within blocks), the reward for correct performance was withheld. Movement direction requests for flexion and extension movements were given in groups requiring 10 correctly executed trials each. In any case, monkeys began the next trial by returning the handle position to the center zone. The neuronal activity during rewarded trials was compared with that during trials immediately following a withheld reward for corresponding flexion and extension movements. Comparison was made between groups of trials in which Reward and KR are predictable vs. unpredictable. Temporal and magnitude assessments of stimulus-related and premovement and movement neuronal activity were conducted to determine whether these activities were enhanced or suppressed in the rewarded trials as compared with the trials following those that were not rewarded and in trials where direction was predictable vs. unpredictable.

Data analysis.

Data analysis was conducted in several stages. Graphic and numerical displays of the neuronal activity and wrist position were reconstructed by an off-line data analysis routine. Peri-event histograms, raster displays of the neuronal activity, and analog displays of the animal's behavioral performance also were examined. These displays were oriented in time either with the onset of the sensory stimulus (go-cues) or with the onset of the sensory triggered movements.

Activity Measurements-

The level of background activity for each set of trials was designated as the mean discharge rate during the hold period (measured in spikes/s) and was compared to the mean discharge rate of all subsequent phases of the task that precede movement. Neuronal activity associated with sensory stimulus onset was measured by determining the first monotonic change in activity after stimulus onset in which the magnitude of the activity was statistically different from background. Premovement activity was measured from displays centered on movement onset using the same temporal and magnitude criteria. Premovement activity was designated as the first significant activity change following the return to background after any (if present) go-cue related response and continuing until movement onset. Several statistical methods for determining significant changes in neuronal activity were available. The one that we used most often was the conversion of the data to a cumulative sum (CUSUM) record from which, the first change in mean firing rate which was ± 3 SDs from the background level served as the onset of significant change. Cue-related and premovement activity magnitude changes was compared by subtracting the background activity from each. Times of activity changes (onsets) were temporally referenced to important behavioral events. Stimulus related events such as onsets and offsets of instructions and stimuli were entered into the data stream. Moreover, movement related events such as movement onset from center, first target acquisition

and movement onset from target back to center were recorded. Thus, we determined if neuronal activity, averaged over up to 40 similar trials, was temporally correlated with, and preceded or followed stimulus and movement related events.

Kinematic Measurements-

RTs and MTs were measured by conventional means. For certain comparisons of activity modulation it was necessary to restrict consideration to trials, under differing behavioral conditions, which had similar kinematics. Handle position was continuously sampled. We are currently able to differentiate this signal using the off-line analysis routine, smooth the resulting velocity trace with a nine-point smoothing algorithm and calculate 1) peak velocity, 2) time to peak, 3) time to next zero-crossing after movement onset, 4) occurrence of trial completion and 4) the number of peaks in the velocity trace, for each behavioral trial. When we wished to define similar kinematic conditions, we restricted the trials examined by RTs and MTs and the variables above using the same routine. Mean values were calculated for one or more of the above. Similar kinematics were defined as being with a 95% confidence interval for those calculated parameters under the behavioral conditions in question. In our experience, monkeys normally make stereotypic movements in these paradigms, irrespective of changes in behavioral conditions. Only RTs and MTs seemed to vary.

Comparison of Group Data-

Once onsets, offsets and magnitudes of activity were determined, the results were compared quantitatively and qualitatively. All records will be grouped by the anatomical location of recording sites and any of the several category variables listed above. Analyses of variance (ANOVA) were conducted on all possible combinations. Dependent variables to be examined first included mean background activity, cue response magnitude, movement associated activities, reaction times and movement times. The data were split only by those independent paradigm and activity variables that had a significant influence over the dependent variables in the experiments. Comparisons of groups by anatomical location were conducted. Group statistics were conducted using either parametric or when appropriate, non-parametric procedures since the was no *a priori* reason to assume that the distributions were evenly distributed or of equal number. By these methods we determined group mean onset times for cue and movement associated activity changes and determined which of the experiment manipulations had significant influences over the firing patterns of sensorimotor cortical neurons.

Experimental Methods - Human Psychophysical Studies

Adult volunteers (ages 20-45yrs) performed the paradigms described below. They performed the tasks with their preferred hand. All had normal or corrected-to-normal vision and normal hearing. These subjects received no compensation for participating. Selection of volunteers did *not* involve preferential inclusion nor exclusion of women and/or minorities since only age was germane to the subject population.

Subjects were seated in a specially designed chair in a quiet, moderately lit (5 foot-candles) room and view a display panel placed 50cm directly in front of them at eye level. This display contained 31 light-emitting diodes (LEDs) located behind a smoky-grey acrylic plate. The details of this display are described above. The subject's hand rested on a flat aluminum handle coupled at one end to the axle of a brushless DC torque motor while the forearm was supported by an arm rest.

The paradigms used was essentially similar to those described above for the animals. Go-cues and/or targets for new wrist position remained on until the subject moves to align the wrist position cursor

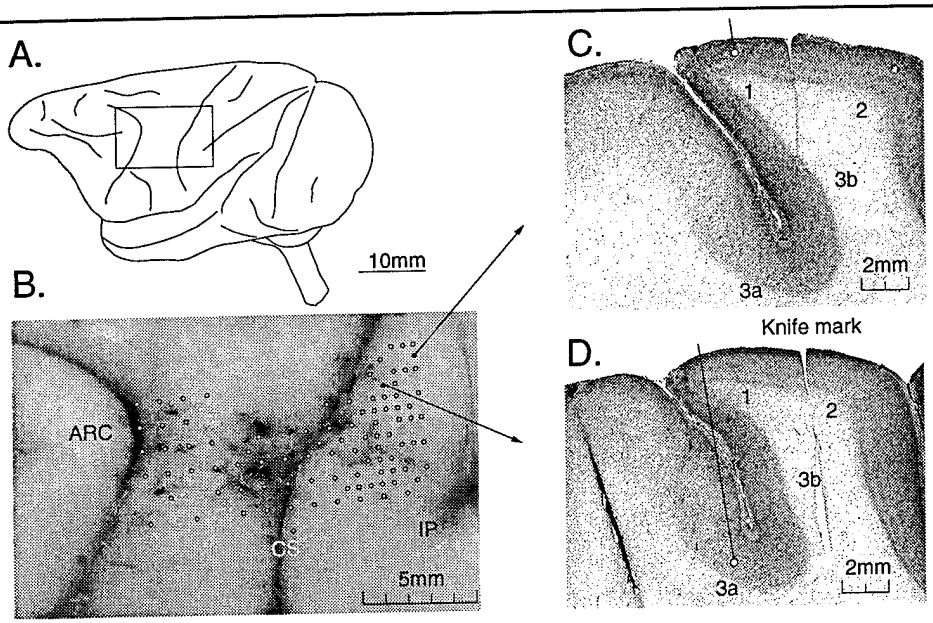


Figure 1. A. Drawing of the dorsolateral surface of the brain of the most extensively studied monkey. B. Recorded region as marked in box in A. Circles indicate surface location of penetrations. C. Location of the area 1 neuron whose recordings are illustrated in Figure 2 and 3. D. Location of the area 3a neuron whose responses are illustrated in Figure 4. To date, all recording locations from the 327 task-related neurons from 2 monkeys have been reconstructed. A third experiment is currently in progress. ARC= Arcuate, CS=Central and IP=Intraparietal Sulci. Shown are calibration marks for reconstruction.

with the target, holding the handle in the target position for 0.5-1.0 s. On the first training day each subject were instructed to make wrist flexion and extension movements as quickly as possible without sacrificing movement accuracy (when required). Subjects were asked to perform their task during 14 individual sessions separated by not less than one nor more than four days. The speed and amplitudes of movements was not restricted other than by stops in the apparatus at ± 30° of angular deflection from center. A trial was considered a failure if the subject "overshot" the target by <1.0° in an attempt to acquire that target, if the subject does not acquire the target within 1 sec of movement onset or if the new position was not held for 0.5-1.0 sec (when necessary).

Data Analysis

Data analysis of RTs and MTs as well as the kinematics of the human performance will be identical to the procedures described above for the animal experiments.

Summary

Each of the experiments described above yielded data that wascompared with previously obtained data from sensorimotor cortical neurons, recorded while monkeys perform the similar tasks. The specific goals of proposed studies were a) to understand the influence of unpredictability of behavioral task requirements and knowledge of results upon sensorimotor cortical activity, b) to understand the special role that these neurons play in sensorimotor integration during the initiation and execution of cutaneous and proprioceptively guided movements and c) to determine if human subjects perform the behavioral tasks in ways that strengthen the contention that neurophysiological events in the primate brain reflect what occurs in homologous regions of the human CNS while performing under the same behavioral conditions. The long-term goal of our work is to better understand the role the sensorimotor cortices play in motor control during stimulus detection and classification, response programming and selection (initiation) and response production (execution). Through an understanding of the normal sensorimotor integrative functions during complex behaviors, new insights can be gained regarding what occurs during sensorimotor behavior under extremely demanding conditions such as supersonic flight.

Preliminary Results-

Six sets of studies, either recently completed or currently underway are specifically relevant to the research previously proposed in USAF GR AFOSR 91-0333. The neurophysiological experiments suggest

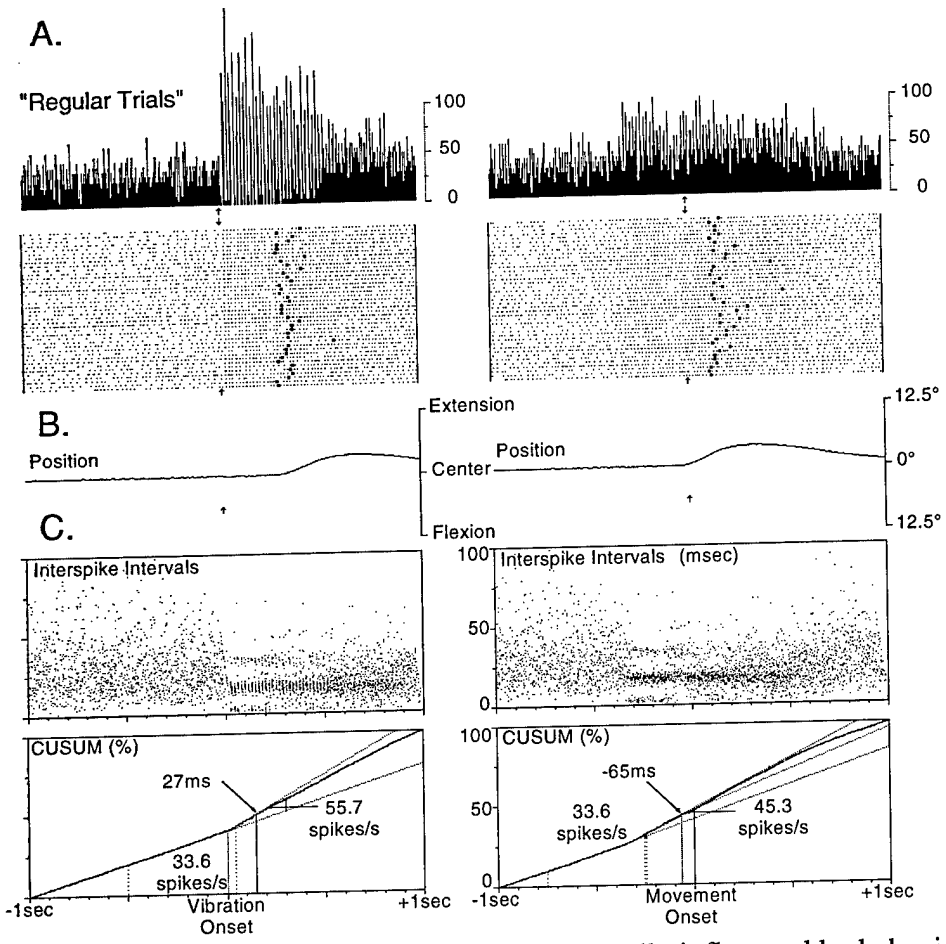
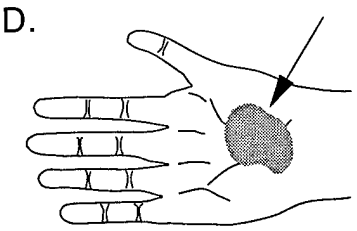


Figure 2. Displays of the parameters, as a function of "behavioral time", centered on vibration onset (left) or movement onset (right). Records are from trials that followed a rewarded trial (regular trials). A) Histograms showing mean firing rates (bin width 5ms). Rasters in which each dot represents a spike and each row represents a single trial. Dark marks indicate movement onset (left) or reward delivery (right). B) average position traces. C) Interspike intervals (ISI) constructed by plotting the ISI of the nth spike in behavioral time. Rhythmic firing appears as horizontal bands. Calculations of firing rates and their onsets using the CUSUM method whereby the slope of the CUSUM is the mean firing rate and deviations of ± 3 SDs for the mean constitute the onset. This Area 1 neuron (see Figure 1C) had a cutaneous receptive field on the thenar pad extending to the hypothenar eminence (D).



that the responsiveness of SI neurons is profoundly influenced by behavioral conditions. The human psychophysical experiments suggest that subjects perform in a similar manner to monkeys in behavioral tasks of the type used to study neuronal responsiveness in monkeys.

1) *Sensory Cortical Neuron Responsiveness During The "Unpredictable Task".*

Goals of the Study-

We are currently concluding experiments that test the hypothesis that variations in expectation alter SI neuronal sensory responsiveness and premovement activity. The paradigm used is described in detail in Research Design and Methods. Using an unpredictable reward schedule for correct task performance, we have created a condition under which monkeys sometimes are not reinforced for seemingly appropriate movements. Several results are thought to be possible. In trials immediately following correct but unrewarded performance ("after trials"), both sensory responsiveness and premovement activity may be either enhanced or suppressed. We wished to describe these changes quantitatively and qualitatively.

Brief Description of Methods-

Three monkeys were trained to make wrist flexion and extension movements in response to vibratory and/or visual go-cues. We are currently recording from the third of these. Each monkey first held a centered wrist position and awaited the trial's go-cues. Upon receipt of that cue, he made ballistic wrist flexion or extension movements, in blocks of ten. Using a pseudo-random reward schedule, we created a condition in which behavioral outcome could not be reliably predicted. About 75% of the trials in which the monkey performed correctly were rewarded. The other 25% were not. The activity patterns of 327 task-related neurons have been studied in detail. A total of 68/327 were vibratory responsive. Vibratory

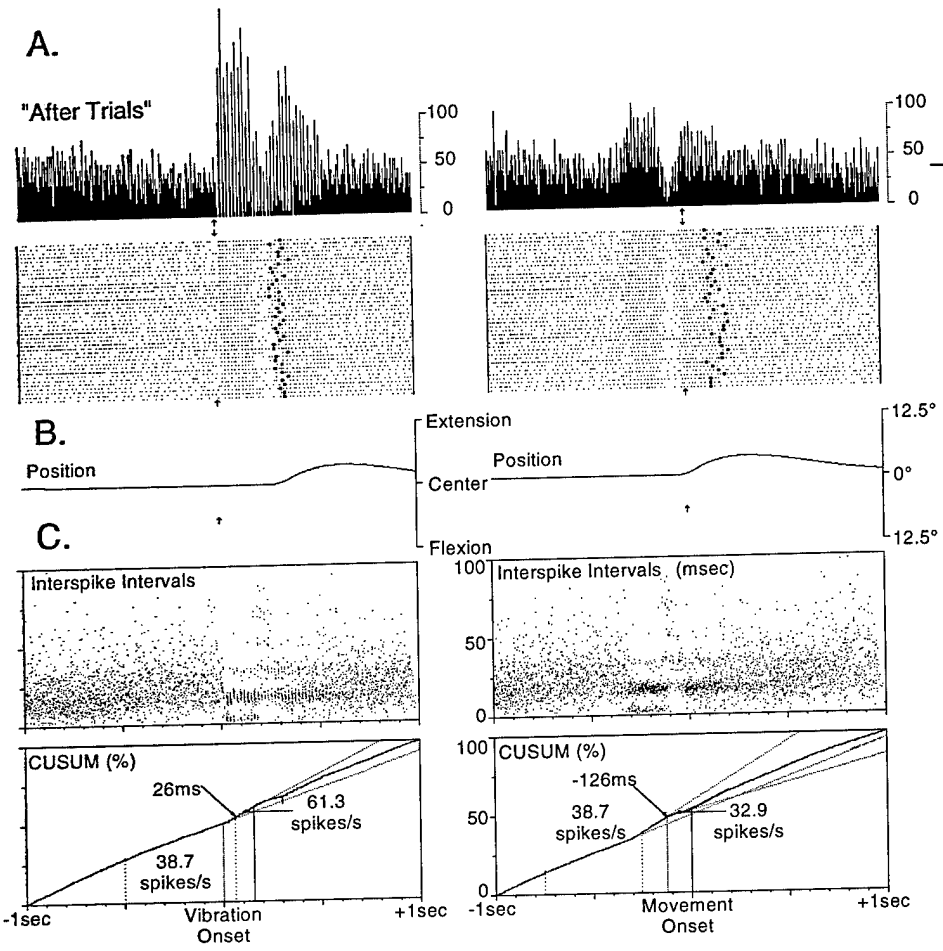


Figure 3. Conventions as in figure 2. Activity of the same neuron except that records show firing associated with trials that immediately followed withholding of reward for correct behavior (after trials). This and the previous figure were constructed from peri-event records associated with vibratory-cued wrist extension movements.

responsive neurons exhibited sustained or transient changes in neuronal activity associated with stimulus presentation. Of these, 14 had Deep and 38 had Cutaneous receptive fields (RFs). Fourteen of these neurons were lost before an RF could be determined and for two, no RF was found. A total of 314/327 exhibited premovement activity. From these, 300 were selected for reasons described below. Of these, 40 showed reciprocal, 67 exhibited unidirectional and 193 had nondirectional premovement activity patterns. Locations of penetrations in the most extensively studied monkey are shown in Figure 1.

Results-

Neuronal activity during rewarded trials (Figure 2) was compared with that for after trials (Figure 3) when monkeys made similar wrist movements. Often, qualitative differences in the activity patterns of these SI cortical neurons during "regular" (rewarded) and after trials were readily noticeable. For example, compare the activity occurring ~100ms before movement onset in Figure 2&3. In initial quantitative examinations, we calculated the premovement activity (PMA) magnitudes and onsets of magnitude changes for all neurons. Using a modified version of the Cumulative Sum Method (CUSUM) and paired t-tests to determine significant differences measurements for neurons within each cortical region studied, we analyzed 300/327 neurons which 1) had significant changes in PMA magnitude prior to movement in at least one direction that 2) occurred between 20-250ms before movement onset. Figure 5G shows results that indicate that PMA magnitude and onset for the regular and the after trials appear to be distributed in two statistically different populations. In panels A-E of this figure, the distribution of the enhancement indices (EIs; after trials PMA magnitude / regular trial PMA magnitude) are presented. This figure also shows the distribution of recorded neurons by cortical location and RF type.

From these initial PMA analyses, we have developed working hypotheses to guide subsequent experiments. First, and in general, in trials triggered by vibratory but not as consistently by visual cues, PMA onsets occurred earlier in regular as compared with after trials (Figure 5G). Thus, PMA changes occur nearer movement onset when the behavioral conditions are less predictable. Second, PMA magnitudes are greater during after trials than during regular trials. The mean EIs are often greater than unity and indicate that statistically significant changes in PMA may be, on average, 12-48% greater in after trials. The broad distribution of these EIs may be explicable once we have additional data so that we can conduct

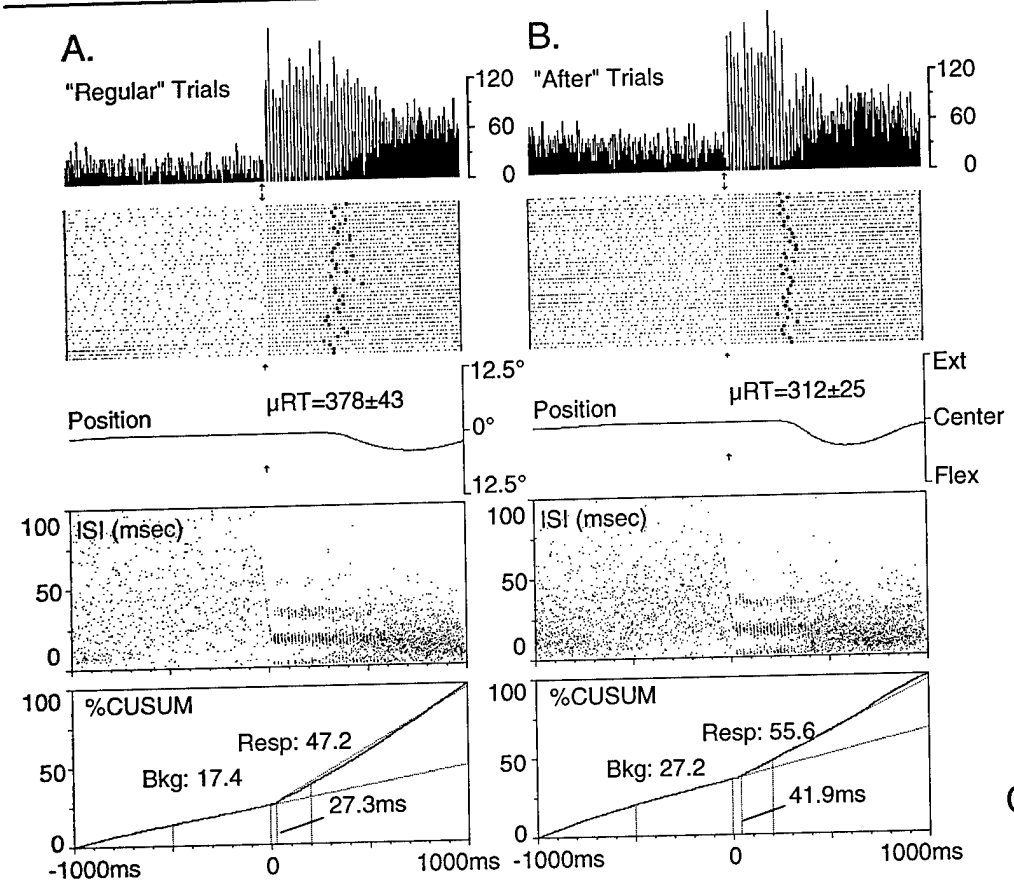
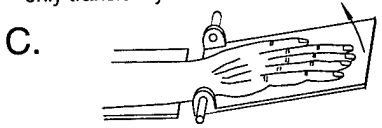


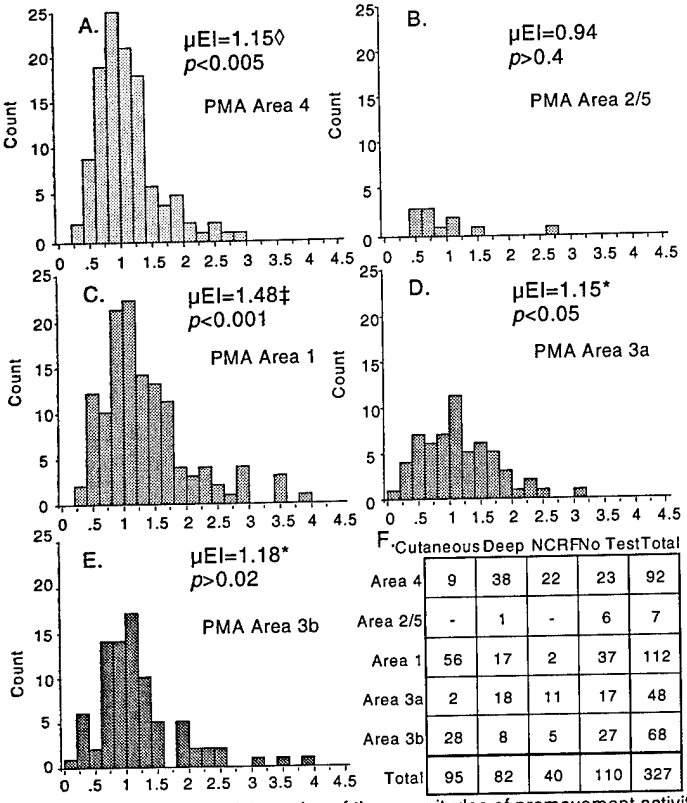
Figure 4. The vibratory responses of an Area 3a somatosensory cortical neuron (C and Fig. 1D) recorded during the performance of regular (A) and after trials (B). Measurements of the mean firing rate during the 500ms of active holding against the load (Bkg; background activity) are given below, to the left of the arrow, which indicates vibration onset, in each of the panels. Values above the arrow the lower panel indicate the mean firing rate during the first 150ms following the onset of the 57 Hz vibratory stimulus which served as the go cue for flexion or extension (not shown) movements. Each was calculated using the CUSUM method whereby the slope of the CUSUM is the mean firing rate. Also listed are mean reaction times (RT) ±SD (upper panels). In general, background activity was greater in after trials than in the regular trials. Vibratory response during the first 150ms after stimulus onset was often greater than in the regular trials. RTs where faster and more consistent in after trials. Mean values for these parameters are listed in the following figure. The neuron was recorded at a depth of 7.8mm from the cortical surface (see Figure 1D). It responded to passive wrist extension (C) and palpation of the flexor carpi ulnaris. It showed similar entrainment at 27Hz, but responded only transiently to 127Hz vibration.



a detailed analysis of EIs for each RF type for each cortical area. In addition, more data is crucial for our ability to make statements regarding changes in activity in more posterior somatosensory cortical areas (areas 2 and 5) during this paradigm.

We have analyzed, in detail, the activity patterns of 68 vibratory-responsive neurons (see Figure 4). Our findings indicate that these sensorimotor cortical neurons tend to be more responsive to peripheral stimuli in after trials as compared with regular trials (Figure 5G). The statistically significant increase in mean firing rate (MFR) in after trials may be due to tonic increases in excitability as indicated by increases in background activity. When MFRs are normalized by subtracting background activity (Figure 5G ΔPMA) these differences loose statistical significance. We also observed that RTs in after trials were shorter and less variable than in regular trials. These final observations are consistent with hypotheses made previously about what might occur if addition selective attention were directed toward the task.

Sensorimotor neuron modulation in "after" trials appears to continue long periods of time with change. This contention can be made in two ways. First, within a block of trials, one or more measures of activity may systematically vary due to adaptation to the partial reward schedule. This doesn't appear to be the case. Figures 2-4 are presented such that "regular" and "after" trials are ordered chronologically from top to bottom in the raster displays. No significant serially dependent variations in background, vibratory-related activity, nor premovement activity (PMA) are evident upon visual inspection in these nor in over 98% of the 327 cases examined. Over 10% of these have been examined using the Wald-Wolfowitz Runs Test to determine of there is any serial order to the magnitude of changes in activity, as a function of trial type, during background, cue and premovement epochs. No significant differences have been found. Second, the magnitude of the effect(s) may vary as function of recording session, thus indicating a long-



F.

	Cutaneous	Deep	NCRF	No Test	Total
Area 4	9	38	22	23	92
Area 2/5	-	1	-	6	7
Area 1	56	17	2	37	112
Area 3a	2	18	11	17	48
Area 3b	28	8	5	27	68
Total	95	82	40	110	327

G. Visually -Cued Trials

Premovement Activity (PMA)

	N	Reg. Onset	After Onset	ΔBKG	ΔOnset	ΔMFR	ΔPMA
Area 4	117	169±62	159±63	1.05	1.19◊	1.08*	1.12◊
Area 2/5	-	-	-	-	-	-	
Area 1	71	107±47	103±53	1.04	1.86	1.14*	1.27*
Area 3a	46	122±47	127±53	1.18‡	1.21	1.11◊	1.22*
Area 3b	37	86±42	85±45	1.04*	1.24	1.04	1.09

Vibratory -Cued Trials

Premovement Activity (PMA)

	N	Reg. Onset	After Onset	ΔBKG	ΔOnset	ΔMFR	ΔPMA
Area 4	116	177±56	160±60	1.37◊	1.02	1.10◊	1.15◊
Area 2/5	11	149±64	150±61	1.10	1.04	0.94	0.98
Area 1	131	137±59	129±59	1.17‡	1.21*	1.16◊	1.48‡
Area 3a	59	134±52	125±50	1.15*	1.18	1.12*	1.15*
Area 3b	82	91±44	79±46	1.03	1.10	1.04	1.18*

Cue-Related Activity

	N	ΔBKG	μOnset	ΔMFR	ΔResp.
Area 4	8	1.24◊	49±40	1.00	1.67
Area 2/5	-	-	-	-	
Area 1	53	1.21‡	41±26	1.12*	1.07
Area 3a	21	1.10*	33±21	1.07◊	1.03
Area 3b	30	1.03	37±22	1.01	0.96

Reaction Times (RTs)

	Days	Regular	After	ΔRT
Flex	110	326±43	312±33	13.9‡
Ext	110	330±57	309±45	20.7‡

N=number of cases (1 each for significant change for each movement direction for each neuron). Results different from one by one-factor ANOVA. * = p <0.05; ◊ = p <0.01; ‡ = p <0.005. *Ratio for EIs of Onsets is regular/after value.*

Figure 5. Distributions of the ratios of the magnitudes of premovement activity [PMA (MFR-BKG see below); (A-E)] in after trials compared with during regular trials (Enhancement Index; EI= after trial value/regular trial value). Significant changes in premovement activity during the after trials were ~ 12-48%. F) Table listing the number of task-related neurons analyzed as a function of receptive field (RF) type (upper) and cortical location (left). NCRF=no clear RF; NT=not tested. G) Means and SDs of onsets of activity and Reaction Times (in msec). EIs (=Δ) for background activity (BKG; during the hold phase of the paradigm), MFR (Mean Firing Rate) and PMA for the cases from those neurons having PMA. Below, Δ for the activity of vibratory-responsive neurons during the initial 150ms after vibratory go-cue presentation. RTs are for the entire 110 recording sessions. (see text)

term adaptation to the paradigm conditions. Figure 6. illustrates the enhancement indices as a function of the order of observation, for instances of area 1 neuronal PMA recorded from a single animal. As with all of the other parameters examined, no serial order was found. These observations suggest that the effects continue throughout the duration of the experiment, which may extend to as much as one year of recording.

We are now conducting a similar analysis on over 50 vibratory responsive and other task-related neurons from which we have recently recorded. Initial impressions are that the observations stated above will be confirmed with these additional data.

Conclusions and Comments-

When the predictability of behavioral outcome is unaltered (i.e., when the monkey has previously been rewarded for performing correctly) both sensory responsiveness and PMA in SI neurons are at some baseline level. In trials which follow withholding of the reward for correct performance, outcome predictability is altered. When behavioral conditions become less predictable, PMA (which may reflect either central or peripheral inputs, depending upon when it occurs), and sensory responsiveness appear to be enhanced. However, decreased predictability is associated with later PMA onset, perhaps because of behavioral uncertainty.

These data are open to at least two types of interpretations. We have previously argued that PMA may gate the response of other SI neurons that do not play an important part in the upcoming movement. We have also argued that PMA may reflect a corollary discharge from primary motor cortex (MI) since neurons in SI areas receiving direct MI projections tend to show PMA while those in areas without direct

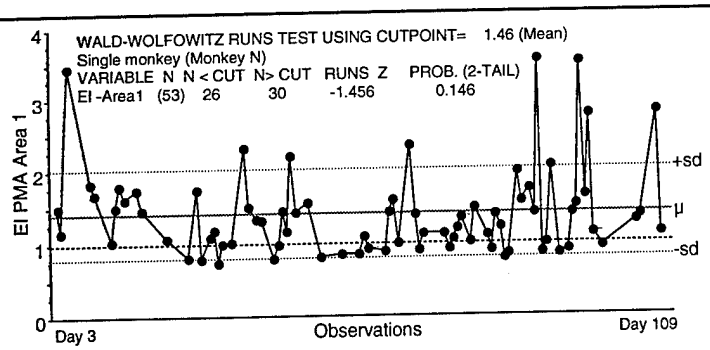


Figure 6. Graph of Enhancement Indices (EI) of Premovement Activity (PMA) for Area 1 neurons as a function of recording session. Shown are the mean for the population (μ) the standars deviation (±sd) and a unity line. The EIs were calculated by subtracting the background activity from the mean firing rate (MFR) for each condition to derive the PMA and then determining the ratio : After Trial PMA/ Regular trial PMA. No serial dependency was demonstrated.

MI projections do not. MI stimulation is known to alter SI neuronal responsiveness to cutaneous and proprioceptive inputs. Finally we have observed in records of the 68 completely analyzed sensory-responsive neurons, that vibratory stimulus-related responses are greater in the after trials. This last observation indicates that during conditions of predictable behavioral outcome, the responsiveness of sensorimotor cortical neurons is attenuated. When performance outcome becomes less predictable, this attenuation appears to be removed. The observation that PMA is, in general, greater in the after trials fits the hypothesis that a general mechanism is responsible for decreases the activity of SI neurons in response to both peripheral and centrally-generated inputs. One possible role for an increase in PMA might then be to suppress or disrupt the activity of other neurons that do not convey important information about the subsequent movements. Another interpretation is that these neurons are themselves the behaviorally important ones and that increased PMA actually reflects increased information transfer, perhaps related to increased selective attention directed toward behaviorally important events. These two roles are not mutually exclusive and probably occur simultaneously.

Regardless of which interpretation is favored, it appears that sensory gating is dependent upon whether there is a reasonable expectation that attenuating some inputs and strengthening others may actually improve performance by removing potentially competitive sources of information coming from the periphery. Further experimentation will determine if cortical location and RF type are important factors determining the effects of reward predictability upon neuronal responsiveness in SI.

2) *Sensory Cortical Neuron Responsiveness Synchronized to Vibratory Stimuli.*

Goals of the Study-

Primary somatosensory cortical (SI) neurons exhibit characteristic patterns of activity prior to initiation of voluntary movements. It is believed that premovement activity in SI neurons may result from centrally-generated as well as peripheral inputs. We examined premovement activity patterns for a group of SI neurons that represent somatosensory peripheral stimuli in a most faithful way. These neurons were characterized by entrainment of their activity to vibrotactile stimuli (i.e., by a very close temporal correlation between the stimuli and the neurons' responses to them). We hypothesized that, for selected neurons, activity patterns of central and peripheral origin can be distinguished. It was expected that central input, if any, might introduce a component into the vibration-entrained neuronal firing that is asynchronous with the peripheral vibratory stimulus. Thus, vibration-entrained firing might have its synchrony reduced at about the same time that other, non-entrained cortical neurons exhibit PMA.

Brief Description of Methods-

Monkeys made wrist flexion and extension movements in response to sinusoidal vibration (27, 57 or 127 Hz) of their palms. Vibration remained on until the animal moved at least 5° from the initial hold (center) position. The activity of 55 extracellularly recorded SI neurons (areas 3a, 3b, 1, 2 respectively: 10, 13, 28, 4) was vibration-entrained. The temporal relationship between the vibratory stimuli and neuronal firing was described by the mean phase (MP) of spikes with respect to the vibratory cycle. The degree of

entrainment was quantified as synchronicity (Sync), which was derived from the standard deviation (SD) of the phase and expressed in units scaled between the SD for non-entrained firing and the SD for a constant response phase. Mean firing rate (MFR) was derived from the number of spikes per vibratory cycle. More complete descriptions of the behavioral paradigm, the electrophysiological recording procedures and methods of data analysis are found elsewhere (See Lebedev and Nelson, 1994; complete reference found under the heading "List of Publications").

Results-

Typically, during the hold phase of the paradigm preceding vibration onset, neurons with either cutaneous or deep receptive fields (RFs) exhibited background activity. The background firing rate was, on the average, larger for units with deep RFs (mean=30.2 spike/s) than for units with cutaneous RFs (mean=21.5 spike/s). After a transitory burst in response to vibration onset, the studied neurons responded to the ongoing vibration in a steady-state manner. During this period of stabilized response, which was usually about 100 ms in duration, neuronal firing was entrained to the vibratory stimulus. For some neurons, MFR of the stabilized response was not substantially different from background MFR. Thus, the characteristics of peripheral input were coded by the temporal firing pattern rather than by MFR. For neurons with deep RFs at all tested vibratory frequencies, and for neurons with cutaneous RFs at 27 and 57Hz, MFRs were not significantly different (mean=46.4 spike/s). At 127Hz, for neurons with cutaneous RFs, MFR decreased (mean=19.4 spike/s).

For the majority of cells, the pattern of stabilized response was modulated prior to movement onset. Cases of MFR increase (premovement activation) and of MFR decrease (premovement suppression) were observed. Also, two premovement changes in MFR often were observed (two-event cases). For two-event cases, early and late MFR changes could be distinguished. In many cases, premovement changes of MFR began before EMG onset, suggesting that this modulation results from centrally-generated inputs rather than from movement-associated peripheral reafference.

Premovement activation was accompanied by shifts of mean phase towards earlier responses to the ongoing vibratory stimulus, and by a decrease of response Sync. The correlations of the onset of MFR increases with these shifts in MP and Sync were statistically significant. The desynchronization was more profound at the lower vibratory frequency (27 Hz) when compared to higher ones (57 and 127 Hz). However, MP shifts were more prominent at the higher vibratory frequencies. We suggest that, during premovement activation, an asynchronous signal is integrated with the periodic peripheral input. This asynchronous signal may make neurons more likely to discharge and to do so earlier with respect to the vibratory input. The asynchronous component may also disrupt the vibration-entrained activity pattern. Several observations lead us to suggest this working hypothesis. First, the degree to which the firing patterns of primary somatosensory cortical neurons were synchronized with on-going peripherally-delivered vibratory stimuli could be calculated and expressed as a scaled parameter. Second, the value of Sync often decreased prior to movement onset. This was in spite of the fact that the time at which these decreases occurred often preceded any detectable peripheral positional or muscular (EMG) activity changes and that the firing rate actually underwent an accompanying increase (figure 8 in Lebedev and Nelson, 1994). Third, premovement activity changes in entrained SI neurons occur at approximately that same time as activity changes in non-entrained SI neurons. These activity changes in non-entrained neurons are themselves, not in synchrony with the peripheral stimulus frequency, suggesting that in these neurons, PMA is not merely a late vibratory stimulus related activity. Finally, the activity of entrained neurons was not desynchronized at that time following vibratory stimulus onset when animals are instructed to withhold movements in response to the

same stimuli that have previously served as go-cues in the movement paradigm. Thus, as a working hypothesis, we continue to suggest that it may be possible to distinguish between the response to periodic peripheral stimuli and an input which does not possess the same periodicity and which, by virtue of the fact that responses to it occur prior to EMG and positional changes and are associated with impending movement, may be central in origin. Thus, differences in MP and Sync changes at different vibratory frequencies probably reflect the interaction between the temporal properties of these inputs. We are just beginning to model the possible interactions between inputs of known frequencies, such as those presented peripherally, and those that might arise centrally, such as those which may reach neurons of this type from rhythmically firing neurons in cortical or subcortical structures (see below). What seems clear is that additional inputs to these neurons would tend to make them fire earlier with respect to external stimuli, but also desynchronize their responses to on-going peripheral periodic stimuli.

Premovement suppression was not associated with consistent shifts of MP and Sync. The cases of premovement suppression commonly had larger MFRs during stabilized responses than the cases of premovement activation (e.g., at the vibratory frequency of 57Hz, for one-event patterns, mean value of MFR during stabilized responses for cases of suppression was 56.2 spike/s, and for activation it was 32.0 spike/s).

The onset times of premovement changes in MFR, MP and Sync were compared with RTs for each animal. For animals with longer RTs, premovement events occurred earlier relative to movement onset. Such a relationship is unlikely for peripherally-induced events. The dependence of premovement modulation onset upon RT was more prominent for earlier than later activity changes.

The variability of the firing characteristics associated with the direction of subsequent movement was estimated. This was done for the activity during the stabilized response period and the later premovement period by examining the flexion-extension activity differences. For the stabilized response period, these difference values (for MFR, MP, but not for Sync) were significantly larger for neurons with cutaneous RFs. For the premovement period, modulation patterns substantially varied depending on movement direction. These premovement patterns were classified as reciprocal or symmetrical with respect to movement direction. For two-event cases, early events were more often symmetrical than late events.

Conclusions and Comments-

We conclude that the activity patterns of SI neurons that most faithfully represent the sensory periphery are modulated prior to voluntary movements. We suggest that inputs of central origin contribute to this premovement modulation. Presumably, the role of the central inputs may be to prepare the sensory cortical areas for changes in activity (reafference) that result from voluntary movement.

3) *Sensory Cortical Neurons Which Fire Rhythmically During Active Holding Against a Load.*

Goals of the Study-

Much attention has recently been devoted to examining rhythmic activity in the mammalian neocortex and thalamus. This is due in part to theories regarding the possible functional role of these rhythms in the gating of the thalamocortical transmission of information and/or in switching between different behavioral states. In earlier studies, we had observed single sensorimotor cortical neurons that fired rhythmically, most notably during the period in which monkeys held a handle steadily, against a load, and awaited a vibratory go-cue that triggered stereotypic wrist flexion and extension movements. Our goal was to determine if these neurons showed profound changes in firing rate during this task and, if so, did these changes occur in relation to specific behavioral events or the transitions between different parts of the task.

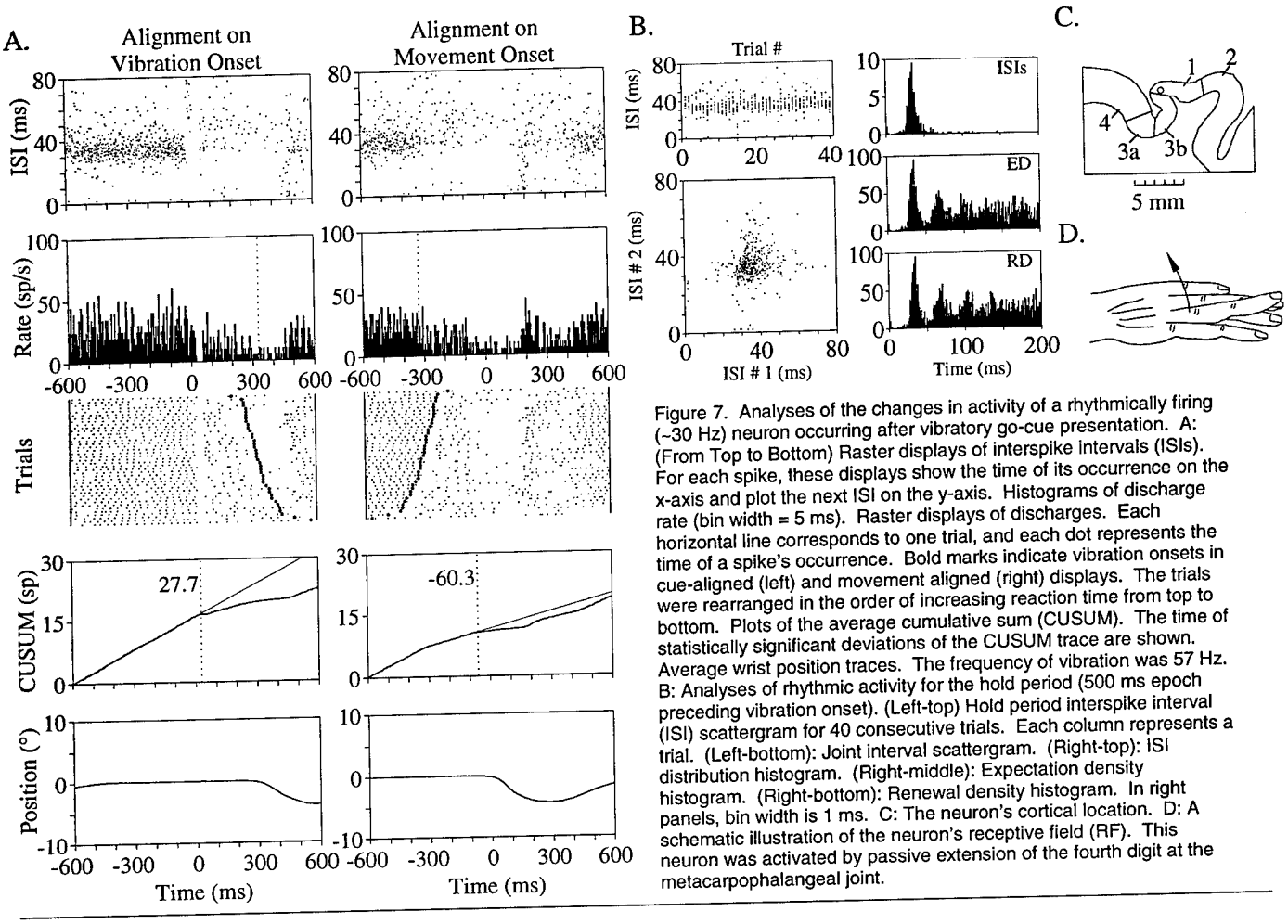


Figure 7. Analyses of the changes in activity of a rhythmically firing (~30 Hz) neuron occurring after vibratory go-cue presentation. A: (From Top to Bottom) Raster displays of interspike intervals (ISIs). For each spike, these displays show the time of its occurrence on the x-axis and plot the next ISI on the y-axis. Histograms of discharge rate (bin width = 5 ms). Raster displays of discharges. Each horizontal line corresponds to one trial, and each dot represents the time of a spike's occurrence. Bold marks indicate vibration onsets in cue-aligned (left) and movement aligned (right) displays. The trials were rearranged in the order of increasing reaction time from top to bottom. Plots of the average cumulative sum (CUSUM). The time of statistically significant deviations of the CUSUM trace are shown. Average wrist position traces. The frequency of vibration was 57 Hz. B: Analyses of rhythmic activity for the hold period (500 ms epoch preceding vibration onset). (Left-top) Hold period interspike interval (ISI) scattergram for 40 consecutive trials. Each column represents a trial. (Left-bottom): Joint interval scattergram. (Right-top): ISI distribution histogram. (Right-middle): Expectation density histogram. (Right-bottom): Renewal density histogram. In right panels, bin width is 1 ms. C: The neuron's cortical location. D: A schematic illustration of the neuron's receptive field (RF). This neuron was activated by passive extension of the fourth digit at the metacarpophalangeal joint.

Brief Description of Methods-

The analyzed data were taken from neurons recorded, but not described, in previous studies. Interspike interval, expectation density and renewal density histograms were constructed to determine the frequency of the rhythmic discharge during the time that the animals held a steady wrist position against a load for at least 500msec, the stationarity of the rhythmic firing and the presence or lack of serial dependence. The onset of changes in mean firing rate, relative to behavioral events such as vibratory go-cue onset and movement onset were determined using cumulative sum (CUSUM) plots in which these onset were detected as changes in the inclination of the CUSUM of more than 3 SDs for at least 40msec consecutively.

Results-

A total of 129 SI neurons (31, 40, 47 and 11 from areas 3a, 3b, 1 and 2) were selected because expectation density (autocorrelation) histograms of their firing patterns during the hold period had peaks at multiples of the mean interspike interval (ISI). An example of one such neuron and the types of analyses normally conducted are shown in Figure 7. Changes in firing patterns from background levels (MFR 32.1±5.4 spike/s) occurred often, following vibration onset for these (67/129) SI neurons. SI activity changes at vibration onset were typically brief firing rate suppressions (60/67). Movement-associated suppressions or facilitations occurred for each of these SI neurons (n=129), but usually didn't vary as a function of subsequent movement direction (84/129 symmetrical; 45/129 directional). For these SI neurons, facilitatory and suppressive influences disrupted rhythmical firing patterns rather than modulating mean ISIs. The mean onset of changes in rhythmic activity that preceded movement onset was 57.4±44.1. ISIs for these SI

neurons, and thus their firing patterns, were regularly and narrowly distributed. Of those neurons with confirmed RFs (n=72), the majority (49/72) had deep RFs while only 23/72 had cutaneous RFs. The similarity of the Expectation Density and the Renewal Density plots (i.e., multiple peaks at regular intervals of approximately the same height) indicates that the source of the rhythmic driving of this neuron is relatively secure in its frequency. However, it does not unequivocally indicate whether this neuron is an intrinsic oscillator or is driven by a synaptically secure source.

Conclusions and Comments-

Some investigators have suggested that rhythmic neuronal firing may be due to intrinsic oscillatory properties while others consider secure external driving to be necessary. However, the precise role of rhythmic activity in sensorimotor integration is not known. Observations have lead authors to seemingly mutually exclusive conclusions regarding its function. It has been stated that oscillatory activity and/or rhythmic firing 1) is encountered more frequently in MI, than SI, 2) is encountered more often in sensory, than non-sensory regions, 3) is often reduced by tactile stimulation or self-initiated movements, and 4) may facilitate interactions between neurons during movements in which selective attention to sensory motor integration is needed. Clearly, more investigation of the behavioral conditions under which rhythmic activity occurs and the events resulting in its disruption is necessary. Regardless of what causes rhythmic firing, SI neurons change activity at times consistent with the hypothesis that they are involved in switching between behavioral modes. (This work is *In Press* and detailed in Enclosure #1).

4) *Responses of Neurons Sensitive to High Frequency Vibratory Stimuli-*

Goals of the Studies-

The "Pacinian Channel" is thought to be important for information processing during active touch as well as during controlled motor behaviors because peripheral elements of this channel are extremely sensitive to minute changes in the tactile environment. As such, signals presented which selectively activate this channel have the benefit of being processed quickly and have the capacity of interupting attention directed to other tactile inputs. Higher frequency (above ~100Hz) vibratory stimuli active receptors at very low thresholds. Thus, as a means of delivering warning cues to a subject already engaged in motor behavior of the stimulated extremity, vibratory signals have distinct advantages. A better understanding of how the central nervous systems processes high frequency vibratory inputs can be gleaned from studying the responses of primary somatosensory cortical neurons to these signals when they are of behavioral importance.

Brief Description of Methods-

The neurons studied where taken from a population collected during but not described in Study #2 (see above). Thus the methods are the same as previously described.

Results-

The activity of high-frequency vibratory sensitive (HFVS) neurons was recorded in monkey primary somatosensory cortex (SI) while animals performed wrist flexions and extensions in response to 27, 57 or 127 Hz palmar vibration or in response to visual stimuli serving as go-cues. HFVS neurons were distinguished by their best responsiveness to the highest frequency vibration (127 Hz) being better than to the lower frequencies. These neurons probably received input from Pacinian afferents. HFVS neurons formed a unique population that constituted ~4 % of the task-related cells, and more frequently were found in areas 3b and 1 (5.3% and 5.4% of the cells recorded in these areas, respectively) than in areas 3a or 2 (1.1% and 2.5%, respectively). Both vibration-entrained and non-entrained HFVS neurons were observed (Figure 8). Discharges of entrained neurons were distributed non-uniformly over the vibratory cycle. In addition, these

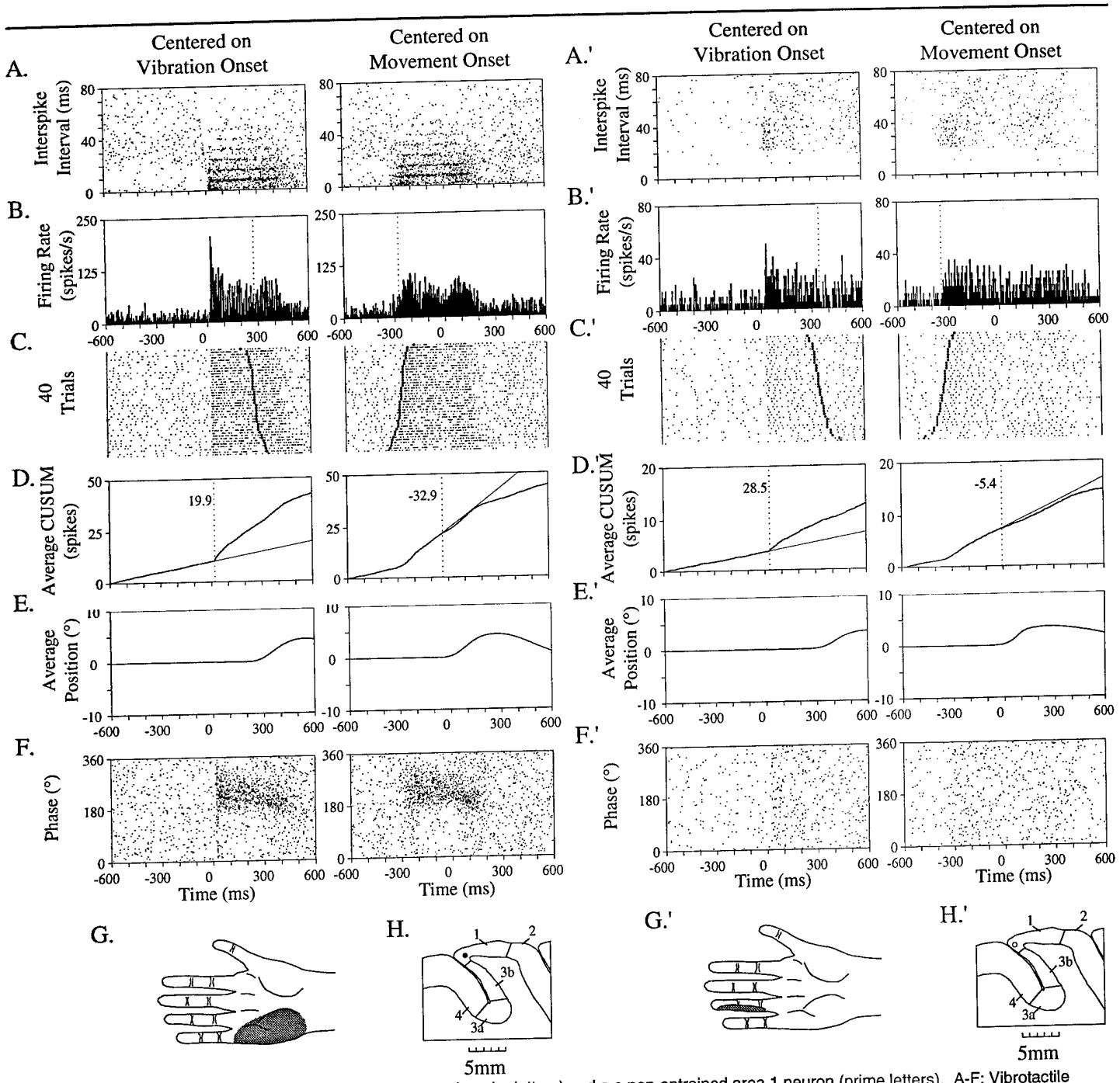


Figure 8. Records for a vibration-entrained area 1 neuron (regular letters) and a a non-entrained area 1 neuron (prime letters). A-F: Vibrotactile stimulation at 127 Hz. Left halves of panels - displays centered on vibration onset; right halves - on movement onset. Onsets of movement and vibration are at zero, respectively. A&A': Displays of interspike intervals. B&B': Histograms of activity (bin width is 5 ms). C&C': Raster displays of activity. Trials are ordered by reaction time. D&D': Average (normalized by the number of trials) cumulative sums (CUSUMs). Significant changes of the slope are marked. Values represent onsets of activity changes. Negative values are before centering event; positive values indicate occurrence after event. E&E': Average position traces. F&F': Displays of spike occurrences relative to the stimulus phase. G&G': Receptive field (RF) schematics. G: The entrained neuron had a cutaneous RF located on the hypothenar eminence while the nonentrained neuron (G') had a cutaneous RF located on the fourth digit. H&H': Schematics of the neurons' cortical locations.

neurons were characterized by multimodal distributions of interspike intervals and negative serial correlations in joint interval scatterplots. Entrained neurons responded to vibration at shorter latencies and with higher firing rates (17.6 ± 4.3 ms and 123 ± 40 spikes / s, respectively, during 127 Hz vibration) than non-entrained neurons (23.9 ± 7.5 ms and 84 ± 44 spikes / s). These observations are consistent with the suggestion that entrained and non-entrained HFVS neurons belong to hierarchical stages of information processing. For these neurons, movement-associated changes in activity occurred earlier than movement onset, but, in most instances (~80%), occurred later than the onset of electromyographic activity of forearm

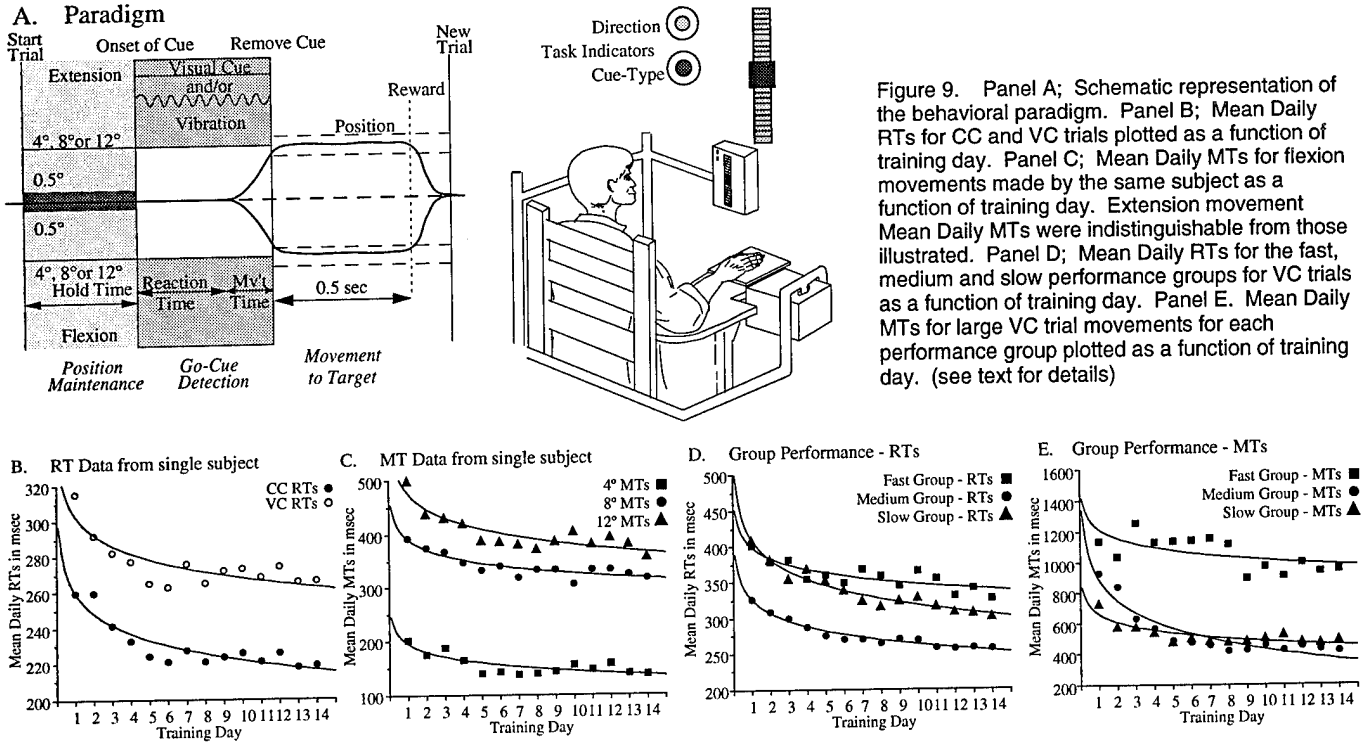


Figure 9. Panel A; Schematic representation of the behavioral paradigm. Panel B; Mean Daily RTs for CC and VC trials plotted as a function of training day. Panel C; Mean Daily MTs for flexion movements made by the same subject as a function of training day. Extension movement Mean Daily MTs were indistinguishable from those illustrated. Panel D; Mean Daily RTs for the fast, medium and slow performance groups for VC trials as a function of training day. Panel E. Mean Daily MTs for large VC trial movements for each performance group plotted as a function of training day. (see text for details)

muscles. Therefore, these activity changes could result from peripheral inputs. However, movement-associated changes in activity were different during vibratory and visually cued trials. During vibratory cued trials, firing rates of HFVS neurons typically decreased prior to the onsets of both flexion and extension movements. However, during visually-cued trials, premovement increases in firing rates occurred more frequently.

Conclusions and Comments-

We suggest that premovement modulation of the vibratory responsiveness of HFVS neurons may result from central gating of somatosensory information rather than mere replication of changes in peripheral inputs (This work was submitted for publication and found acceptable when revised; see Enclosure #2).

5) *Human Reaction Time and Movement Time Experiments-*

Goals of the Studies-

These studies were designed to determine if the performance benefit (shorter RTs) seen with the addition of vibratory cues to visual target presentation is maintained when the amplitude of the required wrist movement is varied unpredictably. Our hypotheses were that 1) RTs for each movement amplitude using combined cues will be significantly shorter than for trials using the target alone, and that 2) MTs for movements between 5° and 15° will not be significantly different as a function of go-cue type, although both similarity and elongation of MTs with increased movement amplitude have been reported.

Brief Description of Methods-

Behavioral Paradigms - General

Adult volunteers performed the paradigms described below. They were asked to perform the task with their preferred hand. All had normal or corrected-to-normal vision and normal hearing. These subjects received no compensation for participating in this study. Subjects were seated in a special chair in a quiet, moderately lit (5 foot-candles) room and viewed a display panel placed 50cm directly in front of them at eye level. This display contained 31 light-emitting diodes (LEDs) located behind a smoky-grey acrylic

Fixed Target Paradigm

Group	CC	VC	Diff (VC-CC)*	
RTs				
Fast (N=8)	218.2 ± 5.3	272.1 ± 6.1	53.8	p=.0001
Med (N=2)	273.7 ± 11.0	310.0 ± 10.2	36.3	p=.0001
Slow (N=2)	282.3 ± 4.7	337.2 ± 7.5	54.9	p=.0001
MTs (5°)				
Fast	155.3 ± 6.7	157.2 ± 6.4	1.9	p=.0752
Med	166.7 ± 10.8	160.7 ± 12.4	-6.0	p=.0016
Slow	262.1 ± 17.5	265.7 ± 17.8	3.6	p=.0699

Variable Target Paradigm

Group	CC	VC	Diff (VC-CC)*	
RTs				
Fast (N=5)	281.9 ± 9.4	322.6 ± 11.1	40.7	p=.0001
Med (N=1)	274.9 ± 13.8	305.2 ± 16.7	30.2	p=.0001
Slow (N=1)	341.9 ± 23.2	391.2 ± 33.3	49.3	p=.0001
MTs				
Fast				
4°	192.1 ± 12.9	196.7 ± 10.4	4.6	p=.0851
8°	352.4 ± 15.4	340.1 ± 14.8	-12.3	p=.0007
12°	446.9 ± 27.2	430.6 ± 26.1	-16.3	p=.0028
Med				
4°	339.7 ± 42.6	393.9 ± 38.7	54.2	p=.0001
8°	525.4 ± 49.1	531.5 ± 43.2	6.1	p=.4804
12°	658.5 ± 51.1	670.7 ± 61.7	12.2	p=.3973
Slow				
4°	452.2 ± 39.2	426.6 ± 27.4	-25.6	p=.0013
8°	723.6 ± 63.2	673.1 ± 47.5	-50.5	p=.0001
12°	934.2 ± 84.7	873.8 ± 84.1	-60.4	p=.0001

Table 1. Group= Performance Group. * denotes paired *t-test* of values which were averaged across the final five training days to obtain the group values listed above. VC= visual cue only. CC= combined visual and vibratory cues. Listed are final means and standard deviations for the parameters.

Random Target Paradigm

Group	CC	VC	Diff (VC-CC)*	
RTs				
Fast (N=3)	296.0 ± 6.3	321.5 ± 9.2	22.8	p=.0001
Med (N=2)	310.4 ± 13.9	335.8 ± 10.7	15.2	p=.0001
Slow (N=1)	389.4 ± 20.3	418.0 ± 22.7	9.4	p=.0001
MTs				
Fast				
4°	228.2 ± 18.5	227.1 ± 13.4	-1.1	p=.7449
8°	376.3 ± 14.1	359.2 ± 13.9	-17.1	p=.0018
12°	495.1 ± 18.1	479.5 ± 11.4	-15.6	p=.0065
Med				
4°	317.7 ± 25.0	344.4 ± 14.9	26.7	p=.0117
8°	492.9 ± 32.7	480.5 ± 22.3	-12.5	p=.2221
12°	657.3 ± 62.9	641.5 ± 46.8	-15.9	p=.1661
Slow				
4°	300.1 ± 11.9	311.1 ± 12.3	11.0	p=.1041
8°	460.5 ± 19.6	471.6 ± 14.7	11.0	p=.1415
12°	611.3 ± 32.7	571.2 ± 30.3	40.1	p=.0300

plate. The details of this display are described below. The subject's hand rested on a flat aluminum handle coupled at one end to the axle of a brushless DC torque motor while the forearm was supported by an arm rest.

In most respects, the three paradigms used were identical to those described above for the animals. In the first paradigm, the go-cue for movement was either a visual target alone (VC; visual cue) or the visual target *and* a vibratory stimulus (CC; combined cue) delivered to the palm of the hand that is to be moved. Vibratory components consisted of vibrating the handle by driving the torque motor with a low-amplitude sine wave at either 27, 57, or 127Hz. Visual targets consisted of illuminating a lamp away from the center of the display (e.g., a target requiring a wrist movement 5° from center was present at ± 1.7° of visual angle from display center). Either cue (CC or VC) remained on until the subject aligned the wrist position cursor with the target on the visual display, holding the handle in the target position for 0.5-1.0 sec. In each paradigm, the subjects heard a click if a trial's movement was appropriate. This click informed the subject of a successful trial and also served as a signal to recenter the handle to begin the next trial. Initially, each subject was instructed to make either targeted wrist flexion and extension movements as quickly as possible without sacrificing movement accuracy. The speed and amplitudes of these targeted movements were not restricted other than by stops in the apparatus at ± 30° of angular deflection from center. However, a trial was be considered a failure if the subject "overshot" the target by <1.0° in an attempt to acquire that target, if the subject did not acquire the target within 1sec of movement onset or if the new position was not held for 0.5-1.0 sec.

Behavioral Paradigms - Specific

Twelve subjects ran the *Fixed Target Paradigm* in which 5° flexion and extension movements were requested in alternating blocks of 10 trials each. Thus, for each block of trials, the required movement direction and the movement amplitude were known. Seven subjects ran the *Variable Target Paradigm* in

Fixed Target Paradigm

Group	CC			VC		
RTs	*const*	α	β	*const*	α	β
Fast (N=8)	218.2	55.3	4.8	272.1	85.0	3.0
Med (N=2)	273.7	24.8	1.0	310.0	15.2	0.1
Slow (N=2)	282.3	68.7	4.8	337.2	68.4	5.5
MTs (5°)	*const*	α	β	*const*	α	β
Fast	155.3	47.0	4.7	157.2	52.7	4.6
Med	166.7	36.2	4.8	160.7	43.4	4.7
Slow	262.1	51.1	8.4	265.7	54.6	7.4

Table 2. Group= Performance Group. * denotes groups whose performance could not be fit by Equation #1. VC= visual cue only. CC= combined visual and vibratory cues. *const= Best Performance,* which was the mean for the last five training days. (See Text for details)

Variable Target Paradigm

Group	CC			VC		
RTs	*const*	α	β	*const*	α	β
Fast (N=5)	281.9	56.8	3.8	322.6	64.8	3.2
Med (N=1)	274.9	30.2	2.4	305.2	193.6	12.0
Slow (N=1)	341.9	104.2	3.0	391.2	*	*
MTs	*const*	α	β	*const*	α	β
Fast						
4°	192.1	173.5	3.5	196.7	157.5	4.6
8°	352.4	274.8	3.6	340.1	279.8	3.7
12°	446.9	390.1	3.5	430.6	378.8	3.8
Med						
4°	339.7	328.9	10.1	393.9	212.2	6.6
8°	525.4	585.5	11.4	531.5	525.2	8.1
12°	658.5	810.1	11.5	670.7	668.8	11.2
Slow						
4°	452.2	*	*	426.6	*	*
8°	723.6	*	*	673.1	*	*
12°	934.2	*	*	873.8	*	*

Random Target Paradigm

Group	CC			VC		
RTs	*const*	α	β	*const*	α	β
Fast (N=3)	296.0	47.8	4.2	321.5	47.7	3.4
Med (N=2)	310.4	92.1	3.6	335.8	91.7	3.8
Slow (N=1)	389.4	46.0	7.6	418.0	52.0	6.7
MTs	*const*	α	β	*const*	α	β
Fast						
4°	228.2	61.8	8.6	227.1	49.6	7.5
8°	376.3	59.8	5.3	359.2	41.0	6.0
12°	495.1	87.6	5.5	479.6	71.5	6.8
Med						
4°	317.7	90.0	6.0	344.4	50.6	3.3
8°	492.9	150.5	4.5	480.5	120.6	4.2
12°	657.3	221.4	4.1	641.5	160.7	4.0
Slow						
4°	300.1	84.1	10.1	311.1	48.9	14.1
8°	460.5	107.2	8.4	471.6	74.9	10.2
12°	611.3	158.0	6.3	571.2	127.3	9.0

which 4°, 8° or 12° flexion and extension movements were requested in alternating blocks of 10 trials each. Thus, for each block of trials, the required movement direction was known, but the amplitude of the movement, as indicated by the location of the visual targets, was varied pseudo-randomly. Six subjects ran the *Random Target Paradigm* in which 4°, 8° or 12° flexion and extension movements were requested pseudo-randomly. Thus, prior to the start of each trial, neither the required movement direction nor the amplitude of the movement nor the type of go-cue was known. For the first two paradigms, the two types of cues were randomly presented within blocks for a given vibratory stimulus frequency. Three groups (one for each vibratory frequency) of at least 240 trials were collected daily for 14 days for each subject. For the latter, at least 480 trials were collected daily for 14 days for each subject at one stimulus frequency. The total duration of these manipulations was 30-45 min.

Data Analysis-

In the Fixed Target Paradigm, the independent variables influencing RTs and MTs were go-cue type (CC or VC), the vibratory stimulus frequency component of the CC (27, 57 or 127Hz) and movement direction (flexion or extension). All movements were made to targets 5° from a centered position held at the start of trials. Movement direction was held constant for 10 trials. In the Variable and Random Target Paradigms, movement amplitude (4°, 8° or 12°) became an additional independent variable. For the Random Target Paradigm, only 57Hz CCs were used because neither RTs nor MTs varied as a function of stimulus frequency in the previous two tasks. For each subject, daily mean RTs and MTs were calculated for each unique combination of the independent variables of that task. After all experiments were completed, an analysis of variance (ANOVA) was conducted to determine which independent variables resulted in statistically significant changes in the dependent variables (RTs and MTs). All the results were examined using a K-Means Cluster Analysis to determine whether there were any natural groupings in the results of subjects from the whole population of a given experiment. Once groups were determined, group daily mean RTs and MTs were determined split along those combinations of independent variables that resulted

in significant differences in group RTs and MTs. The results were further analyzed using a non-linear regression model to describe the characteristics of group performance. These characteristics included improvement in performance from the first day, time in days until stable performance and final performance ceiling (shortest RTs and MTs).

Results-

In general, for each task, subjects improved with practice. Figure 9A presents a rendition of the paradigm timing and requirements. Figure 9B&C illustrate examples of the mean daily RTs and MTs for a single subject. For all subjects, RTs and MTs became significantly shorter with practice. Improvement commonly continued from the first training day until stable performance was reached, usually at about the fifth day for RTs and the seventh day for MTs. For each subject, corresponding RTs and MTs for the last five training days were not significantly different from one another (ANOVA; $p>0.05$). Therefore, the RTs and MTs for the last five training days were averaged to yield final mean RTs and MTs for each unique set of independent variables for each subject. All values for the last five training days were subjected to an ANOVA. For RTs, the only significant covariance was with changes in cue-type. MTs varied only with the amplitude of the movement made. Daily mean RTs and MTs were, then, subjected to a K-Means cluster analysis.

The RTs and MTs of subjects that performed the Fixed and Variable Target Paradigms were neatly distributed into three groups. Figure 9D&E show some of the characteristics of the three performance groups. In general, the fast performance group had quick initial RTs and MTs, showed improvement over the first five days, and reached stable behavioral performance which was maintained after this point. The medium performance group initially had slow RTs and intermediate MTs. With practice, their MTs reached the level of the fast group. Their RTs improved, but were still significantly different from those of the fast group. The medium group took somewhat longer to reach stable performance than the fast group (to be discussed below). The slow group had slow initial RTs and MTs, showed meager improvement over a longer time course with respect to the other groups, and ended with final RTs that were not statistically different from the medium group, but MTs that were different for each movement condition. A cluster analysis was also conducted for the results of the Random Target Paradigm. The groups had the same general characteristics as the fast, medium and slow groups previously determined for subjects that performed the fixed and variable target paradigms (Table 1).

Conclusions and Comments-

Each mean daily RTs and MTs from each task show that subjects began movements more quickly during CC trials than during VC trials. This difference appeared to become less as task complexity increased. For the simplest cue movement combination, occurring during the Fixed Target Paradigm where movement amplitude and direction are known before go-cue onset, mean RTs during CC trials were faster by ≈51ms or approximately 20% of the average RTs for the fast group. For the Variable Target Paradigm, where movement direction was know but amplitude was varied pseudo-randomly, RTs differences were ≈41ms or about 15% of the mean RTs values for the fast group. RTs differences were approximately 25ms or slightly less than 10% of the fast performance group mean RTs values for subject that ran the random target paradigm. In this task, neither the movement direction nor the movement amplitude were predictable. MTs varied with movement amplitude but not significantly with cue type. Increased task complexity resulted in both longer RTs and longer MTs for movements of the same amplitude. However, a least for the fast performance group, the differences in RTs and comparable MTs for the variable and random target task (the two multiple target tasks) were not significantly different statistically. The results of these experiments

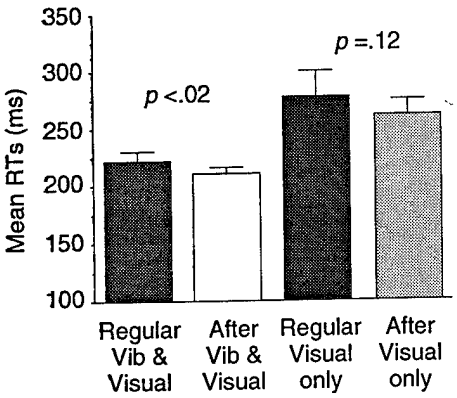


Figure 10. Mean RTs for a subject who performed a paradigm similar to that detailed in Specific Aim #3 for four days. RTs following withholding KR (after) were shorter and the variation (as determined by SD) in RTs was less. Either visual go-cues alone or visual and palmar vibratory go-cues in combination were used.

indicate that visually guided movements are performed more quickly when a vibratory signal to the hand that is to be moved is presented in conjunction with the visual target. They also indicate that movement times, though somewhat faster without the presence of vibratory stimuli that lasts until the target has been reached, are not significantly different as a function of the type of go-cue that a subject receives. These studies suggest that a paradigm of this sort could be used to assess the potential performance of individuals on precision wrist movement tasks. Each performance group has certain characteristics that are evident and expressed in the measured behavior after only a a few days of task performance. Therefore, RTs and MTs collected over only a few days of training may be used to predict the eventual level of performance of which an individual is capable.

Characteristics of group performance were best fit by a non-linear model that can be used to predict some facets of subject performance. We sought to determine if the daily RTs and MTs could be modeled. If this could be done, it was reasoned that given the results of a few days of task performance, accurate prediction could be made about a subject's ultimate performance group, their final RTs and MTs and the time until subjects reach a stable performance level. To model the performance of subjects in each performance group, data were analyzed using the following equation:

$$Performance\ training\ day = Best\ Performance + \alpha * e^{-(Training\ Day\ -1)/\beta} \quad (1)$$

where performance is the variable under consideration, Best Performance is the mean value for the final 5 training days, α is the improvement from first training day until stabilized performance and β is a time constant. However, to predict the level of performance that might be expected on a given training day and hence the percentage of expected total improvement from initial valves may be expressed as:

$$Performance\ level\ [\%\ of\ \alpha] = const + \alpha * \frac{100\% - level\ [\%\ of\ \alpha]}{100\%} \quad (2)$$

Comparison of formulae #1 and #2 gives the following equation for the training day at which a given level of improvement is reached:

$$Training\ Day\ level\ [\%\ of\ \alpha] = 1 + \beta * ln \frac{100\%}{100\% - level\ [\%\ of\ \alpha]} \quad (3)$$

For example, shortening of RTs to within 85% of optimal improvement would be reached at:

$$Training\ Day = 1 + \beta * 1.897 \quad (4)$$

We found that, in general, fast and medium performance groups improve their RTs at similar rates (β) to reach similar stabilized performance levels. MTs continue to be different, however. The exception to this is that very little improvement was observed for the medium performance group during the simplest (fixed target) task. While the slow performance group subjects also improved by about the same absolute value as the other groups, due their their larger starting values, their improvement was actually proportionally less than the other groups. These results are listed in Table 2.

We have just begun to examine the RTs and MTs of subjects in during performance of a paradigm similar to that detailed in Study #1. Initial indications are that subjects exhibit decreases in RTs during after trials, as compared with regular trials, for movement triggered by visual cues alone or visual and vibratory cues in combination (Figure 10). When debriefed following completion of the experiments, naive subjects often reported that they were surprised to have "failed" so often. They also reported that in trials immediately after having failed, they found themselves "trying harder" despite "knowing that they had performed correctly". These anecdotal observations are consistent with the hypothesis that intermittent uncertainty acts as a "wake-up call" which helps to re-focus attention on the task at hand. We will continue to conduct human psychophysical studies to test the efficacy of the paradigms proposed and to make alterations in them when necessary.

Performance predictions may be made using these equations and may be useful in selecting the appropriate individuals for tasks in which the fastest possible RTs and MTs are crucial. These equations may also be useful in determining the duration of training necessary before optimal performance is reached, as well as the extent of motor deficits that accompany neurological and cognitive disorders.

6) *Efficacy of Vibratory Abort Cues in Arresting Previously Triggered Wrist Movements*

Goals of the Study-

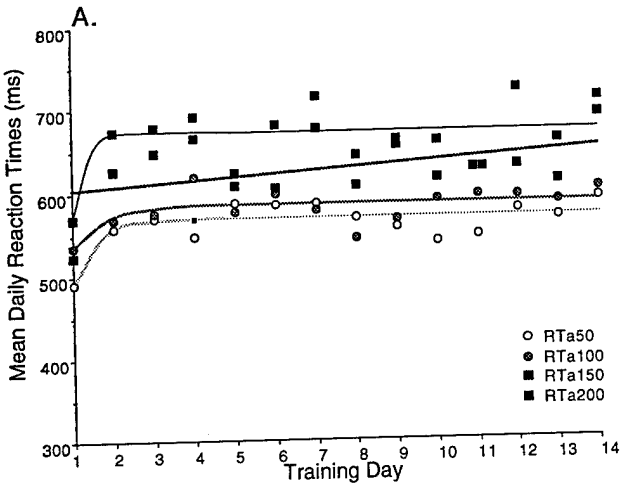
The main objective of this study was to determine the efficacy of abort cues presented at various times prior to wrist movement. It was designed to determine if previously cued wrist movements could be altered by somatosensory signals presented prior to movement. Our working hypothesis is that abort signals presented nearer movement onset must be of greater amplitude to be detected and that abort signal presentation after some crucial point in time may result in the original movement being executed, even though the subjects will indicate that they detected the abort signal either verbally or by making compound movements. In addition, we would predict that the amplitude of the abort cues presented in complexly cued trials would need to be comparatively larger than in visual only trials. This prediction is based upon theories of the nature and occurrence of changes in somatosensory responsiveness to peripheral stimuli that occur prior to movement onset. Finally, we sought to determine if the performance benefit of using vibratory go-cues (i.e., shorter reaction times [RTs]) was maintained for this task. As an initial study, we have conducted the following experiments in which the time of the presentation of abort cues relative to go-cue onset was varied, and their frequency of occurrence was unpredictable. In these experiments, abort cue magnitude was not varied.

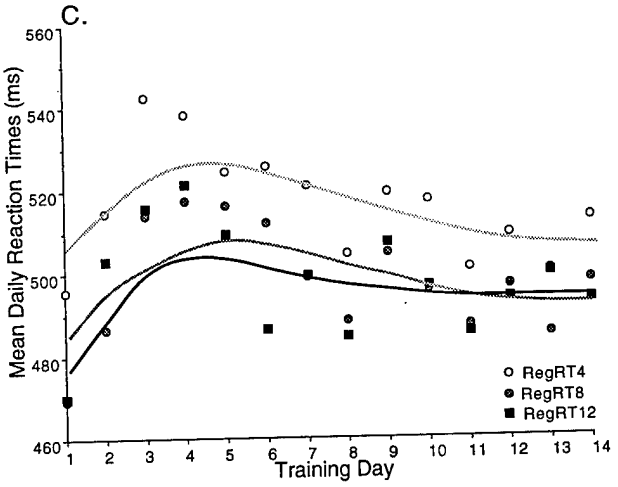
Brief Description of Methods-

Seven adult volunteers performed the paradigm described below. They were asked to perform the task with their right hand. All had normal or corrected-to-normal vision and normal hearing. These subjects received no compensation for participating in this study.

Subjects were seated in a specially designed chair in a quiet, moderately lit (5 foot-candles) room and viewed a display panel placed 50cm directly in front of them at eye level. This display contains 31 light-emitting diodes (LEDs). The subject's right hand rested on a flat aluminum handle coupled at one end to the axle of a brushless DC torque motor while the forearm was supported by an arm rest.

Each trial was initiated when the subject centered the handle so the central LED was illuminated. The handle had a 0.12Nm load assisting extension. At the start of each trial, an instruction LED was sometimes lit. It was located in the upper left corner of the visual display (8.3° of visual angle from the center). The presence or absence of illumination of this LED instructed the subject about the direction of the





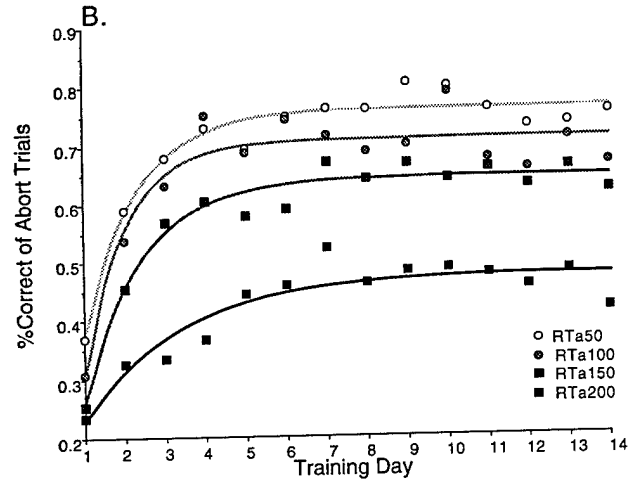


Figure 11. Panel A&C: Mean daily reaction times (RTs) compiled for a population of four human subjects, plotted as a function of training day for abort trials (A) and regular trials (C). RTs were not different depending upon go-cue type (visual only or visual plus vibratory [Combined cue]) nor movement direction. Abort trial RTs were statistically different as a function of the time of abort cue presentation (p=.0001, ANOVA). Regular trial RTs were statistically different as a function of the amplitude of the impending movement (p=.0086, ANOVA). Panel B: Plots of the percentage of abort trials performed correctly, as a function of training day, for each of the four abort cue presentation times relative to the initial presentation of the go-cue for movement. Percentage correct decreased with later abort cue presentation. Said other way, abort trials were less likely to be performed correctly as the presentation time of the abort cues became closer to the time of movement onset. Curves were fitted using the equation: $Y_{(A,B,C)} = \text{const} + \alpha*(1-\exp(-(\text{training day}-1)/t_1))$. Fits for curves in Panel B had R^2 values of 0.953, 0.896, 0.958 and 0.857 for abort times of 50, 100, 150 and 200ms, respectively. Fits for curves in Panel A had R^2 values of 0.622, 0.372, 0.038 and 0.456 for RTs for trials with aborts given at 50, 100, 150 and 200ms, respectively. Data in Panel C could not be fit reliably and so curves were drawn using a Distance-Weighted Least Squares algorithm with tension set to 0.15. All three groups of parameters were significantly different as a function of training day.

required movement (a red LED; on-extension; off-flexion). This LED also warned the subject that a trial had started. The subject maintained a centered wrist position for a randomly chosen period (0.5-2.0sec). If the subject maintained a steady position within ± 0.5° (each lamp = 1°) of center, the current wrist position was designated as the start position for analysis and a go-cue was presented.

Two "go-cues" were used to indicate that a movement should begin. The first (visual cue) consisted of illuminating a target LED on the visual display. The second (combined cue) consisted of the target *and* a vibratory stimulus delivered to the palm of the hand that was to be moved. Vibratory components consisted of vibrating the handle by driving the torque motor with a low-amplitude sine wave at 57Hz or 127Hz (see below). Visual targets consisted of the illumination of the target lamp at 4°, 8° or 12° from center (± 1.7°, ± 3.4°, or ± 5.1° of visual angle). Targets were presented randomly often requiring movement in the direction opposite that from the previous trial. Either cue (combined or target only) remained on until the subject moved to the target. Occasionally (1 in 4 trials; pseudo-randomly determined), subjects received a 127Hz vibratory "abort signal". This was accomplished by adding a 127Hz vibratory signal at various times after go-cue onset. The randomly presented abort signals were presented at 50, 100, 150 or 200ms after stimulus onset. Human movements in response to vibratory stimuli normally have reaction times of approximately 250-350ms in a task that is identical except that abort cues are not presented. Subjects were instructed to move in the direction opposite that originally requested if these signals were detected. Their behavior

served as a confirmation that the signal was detected. Subjects heard a beep if that trial's movement was made in the appropriate direction. This beep informed the subject that the trial was successful and also served as a signal to recenter the handle to begin the next trial. On the first training day each subject was instructed to make the wrist flexion and extension movements as quickly as possible without sacrificing movement accuracy. The speed and amplitudes of these targeted movements were not restricted other than by stops in the apparatus at ± 30° of angular deflection from center. However, a trial was considered to be a failure if the subject "overshot" the target by >1.5° in an attempt to acquire that target. The total duration of daily experimental sessions was about 35-40min. An on-line program operating on a PDP-11/23+ microcomputer was used to control the behavioral paradigms for these experiments and to record the time from stimulus presentation to movement onset (RT; reaction time) and the time from movement onset until the handle position coincided with the target (MT; movement time).

General Results-

We have complete analysis on the reaction times of five of the seven subjects that have participated in these experiments. The data from one subject was not included because this subject failed to master the paradigm even after 14 days of practice. For these ongoing experiments, we have initially examined two types of parameters, 1) the mean daily RTs and, 2) the percentage of correctly performed abort trials. Since it was unclear whether RTs would vary with the impending movement direction and amplitude, go-cue type (visual or combined), or the delay between initial go-cue and the abort signal, several runs of analysis of variance (ANOVA) were conducted. It was found that significant variation in regular trial RTs occurred with the amplitude of the impending movement. RTs during abort trials and the percentage of abort trials correctly performed varied significantly with the time of abort cue presentation relative to the initial go-cue. Each of these three parameters varied significantly with training day.

Mean daily RTs for the four subjects were averaged and plotted as a function of training day (Figure 11C) for rewarded (or regular) trials. In addition, a similar plot was constructed for the RTs of the abort trials (Figure 11A). Finally, the percentage of correctly performed abort trials as a function of training day was plotted for the pooled data from the population (Figure 11B).

It appears that this population of subjects performed the task in a different manner from the performance of subjects on a similar task which lacked abort trials (unpublished observations). That is, combined cue trial RTs were not significantly different from RTs for trials in which the visual target alone was presented. The percentage of correctly performed abort trials initially was very low. In short, it appears that the subjects initially were performing the task as if the abort trials were not present.

With increased practice, subjects seemed to adopt a different performance strategy. Although additional training resulted in increases in the percentage of abort trials correctly performed, RTs became longer until they were ~60ms greater than initial levels.. With further practice, RTs for both types of trials decreased slightly, but were still above initial levels. The percentage of correctly performed abort trials rose steadily during the first 5 training days for trials representing abort cue presentation at each of the four presentation times. After Day 6 there was essentially no further improvement in performance as measured by the percentage of abort trials correctly performed. At this point, relatively consistent RTs were established for both visual and combined cue regular trials, although there continued to be great variance in the the RTs of individual subjects, as well as the population as a whole, as a function of training day.

Upon initial inspection, the percentage of correctly performed abort trials appears to vary inversely with onset of the abort cues relative to movement onset. RTs for individual trials and for individual subjects vary. Therefore, it is impossible to present abort cues at fitted times relative to movement onset. It is possible, however, to choose presentation times for these cues relative to the onset of the initial go-cues and to infer from this strategy what might be occurring as abort cues are presented closer to movement onset. From this reasoning, it appears that movements stand a better chance of being altered if the abort signals are presented earlier in the epoch between initial go-cue presentation and movement onset. In addition, subjects appear to reach stable performance levels earlier for trials in which the abort cues are presented further away from the time of onset of the impending movement. Time constants for the attainment of stable performance are currently being calculated for each subject and will be presented after complete analysis of the data from subjects that have yet to complete the full number of sessions.

Brief Conclusions-

These results suggest that wrist movements can be altered up until a certain point before movement onset, after which, vibratory abort signals may be ineffective, presumably because sensory responsiveness may be gated before active movement. Abort signals of a fixed amplitude are more effective in altering previously requested movement if they are presented as early as possible before movement onset. It will be important in future studies to 1) present fixed amplitude abort cues even later relative to initial go-cue onset to determine if there is a point at which abort signals are no longer perceived, 2) vary the amplitude of the abort signals as a function of time from initial go-cue onset to determine if stronger signals can become more effective in alterning movements and presumably overcoming the peripheral sensory responsiveness decreases that have been demonstrated to occur prior to active wrist movement, and 3) determine if fine control of wrist position suffers from the presentation of vibratory abort cues at various amplitudes and times.

General Statement

The overall goal of the research conducted by this laboratory continues to be to understand the role that behavioral contingencies play in regulating the responsiveness of neurons that are involved in the control of wrist movement. Advances in this understanding make two contributions; the first to our general understanding of how the primate nervous system functions and the second to practical applications for device control.

We have chosen to study SI neurons because of our expertise with these neurons and because of their pivotal position in sensorimotor integration that ultimately results in controlled, goal-oriented behavior. It was previously thought that the responsiveness of SI neurons to peripheral and central inputs was essentially unaltered by behavioral contingencies. Findings from this laboratory and others have suggested that SI neurons undergo sometimes profound and sometimes subtle changes in responsiveness to both peripheral and central inputs. These findings have implications for the understanding of motor control because SI neurons provide direct or indirect inputs concerning limb position and muscle tension to other cortical regions such as posterior parietal, motor, premotor and supplementary motor cortices, as well as to the basal ganglia. All of these structures have been implicated in the control of movement. The demonstration of changes in the responsiveness in SI neurons then implies that the regions mentioned above may receive "pre-processed" information that differs depending upon the behavioral conditions present at any given time. Clearly, to understand motor control, the factors that influence it must be understood, and thus an understanding of the contributions which SI makes to this control are of great importance.

The practical application of this understanding may lead to more efficient design of control systems which utilize changes in wrist position. The results of human psychophysical experiments suggest that the wrist position changes controlling target acquisition may be altered before movements are actually made if vibratory abort cues are presented as early as possible. This may have performance advantages in that movement that are initially warranted and then become either unnecessary or detrimental may be arrested. Caution is warranted and further studies are needed, however, because it has been established that vibratory stimuli can adversely effect wrist position control if the signals are of great enough amplitude. By modeling human RT performance, predictions can be made about an individual's capacity for behavioral improvement and the time course of that improvement.

Status of Future Research

Funding for proposed projects serving as continuation of this work was not provided.

List of Publications

Manuscripts

R. J. Nelson, B. Li, and V. D. Douglas. Sensory response enhancement and suppression of monkey primary somatosensory cortical neurons. Brain Res. Bull. 27:751-757, 1991.

T.W. Gardiner and **R.J. Nelson**. Striatal neuronal activity during the initiation and execution of hand movements made in response to visual and vibratory cues. Exp Brain Res. 92:15-26, 1992.

M.A. Lebedev, J.M. Denton and **R.J. Nelson**. Vibration-entrained and premovement activity in monkey primary somatosensory cortex. (J. Neurophysiol. 72(4): 1654-1673, 1994)

M.A. Lebedev and **R.J. Nelson**. Rhythmically firing (20-50Hz) neurons in monkey primary somatosensory cortex: Activity patterns during initiation of vibratory-cued hand movements. *(In Press*; J. Computational Neurosci., 1995)

M.A. Lebedev and **R.J. Nelson.** Activity of high-frequency vibratory sensitive neurons in monkey primary somatosensory cortex during the initiation of vibratory and visually cued hand movements. (*Submitted*, Exp. Brain Res.)

R.J. Nelson, E.D. Thomas and J.M. Denton. Reaction times and movement times for visually-cued and combined vibratory- and visually-cued hand movements. (*In preparation* for Perception and Psychophysics)

M.A. Lebedev and **R.J. Nelson.** Modulation of rhythmic firing of monkey neostriatal neurons during active hand movements. (*In preparation* for Exp Brain Res.)

Abstracts

R.J. Nelson and T.W. Gardiner. A Comparison of Premovement Neuronal Activity in Monkey Neostriatum and Sensorimotor Cortex. Neuroscience Abst. 17:1218, 1991.

M.A. Lebedev and **R.J. Nelson**. The Activity of Vibratory Responsive Monkey Primary Somatosensory Cortical Neurons is Modulated Prior to Hand Movements. Neuroscience Abst. 18:503, 1992

M.A. Lebedev and **R.J. Nelson.** Modulation of rhythmic firing of monkey primary somatosensory cortical (SI) and neostriatal (NS) neurons during active hand movements. Neuroscience Abst. 19: 781, 1993.

R.J. Nelson, E.D. Thomas and J.M. Denton. Reaction times differ for hand movements made to visual targets alone compared with targets and vibratory go-cues. Neuroscience Abst. 19:545, 1993

M.A. Lebedev and **R.J. Nelson**. Two types of Pacinian-Like neurons in monkey primary somatosensory cortex (SI) studied during active hand movements. Neuroscience Abst. 20:1388, 1994

R.J. Nelson, J.M. Denton and M.A. Lebedev. Activity of monkey sensorimotor (SMC) and neostriatal (NS) neurons during hand movements made under unpredictable conditions. Neuroscience Abst. 20:983, 1994

Associated Personnel

John M. Denton continues to be employed as a Research Assistant. He has, over the four years of this grant, proved to be important in the studies conducted under this grant. He now has expertise in data analysis and behavioral training of monkeys.

Michael A. Lebedev joined the laboratory in the Fall of 1991 as a graduate student following his arrival from Moscow, Russia. He brought to the laboratory an extensive background in mathematics and physics. He was largely responsible for the phase analysis of the vibratory responsive neurons described herein and presented his work at three Annual Meetings of the Society for Neuroscience. He is truly a remarkable individual and has been an asset to the laboratory. Beginning July 1, 1992, he received 50% of his support for funds of AFOSR 91-0333. The other 50% of his support comes from an award by the Center of Excellence in Neuroscience at the University of Tennessee, Memphis. Beginning July 1, 1994, he ceased to receive support from this grant. He attained his doctoral degree in the Spring of 1995.

Erica D. Thomas, a graduate of Christian Brothers University, worked in the laboratory from the Summer of 1991 until the Summer of 1992. She was responsible for analyzing data from human subjects as they performed the psychophysical experiments outlined above. She was diligent in analyzing the data from these rather time consuming experiments and showed some very interesting results with regard to what parameters influence reaction and movement times during hand movements toward a target.

INTERACTIONS

Invited Presentations:

"Set and the Single Simian Somatosensory Cell." University of Montreal December 1993.

"Modulation of sensory responsiveness in somatosensory cortex: possibly by basal ganglia." Montreal Neurological Institute December 1993

Meetings:

1991 Society for Neuroscience Annual Meeting, New Orleans, LA Nov. 10-15
1992 Winter Conference on Brain Research, Steamboat Springs, CO Jan. 25-Feb. 1
1992 Society for Neuroscience Annual Meeting, Anaheim, CA Oct. 25-30.
1993 Winter Conference on Brain Research, Whistler, BC, Canada Jan. 25-Feb. 1
1993 Society for Neuroscience Annual Meeting, Washington, DC Nov. 7-24
1994 Society for Neuroscience Annual Meeting, Miami Beach, FL Nov. 12-17.

NEW DISCOVERIES

None.